From H to F: Strategies in Selective sp^3 C-H Fluorination

BY

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ABSTRACT

The replacement of a single hydrogen atom by fluorine can impart a unique set of chemical and physical properties onto organic molecules, oftentimes modifying their reactivity. In many instances, fluorination improves the metabolic stability of pharmaceuticals, amplifies the electronic properties of polymers, and heightens the efficiency of industrial solvents and surfactants. Despite these and others, fluorination methods have endeavored to become commonplace, a fact consistent with the lack of synthetically mild sources of atomic fluorine. Until recently, fluorination strategies have been predicated upon the use of harsh, unselective, and often destructive sources of fluorine, such as fluorine gas and explosive hypofluorites, limiting their synthetic utility.

Over the last 20 years, the advent of bench-top stable *N*-F reagents have incurred a *renaissance* in the discovery of regio- and chemoselective methods for the direct incorporation of fluorine atoms into organic molecules. In this Dissertation, the applications of one such *N*-F compound, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) is highlighted as a practical reagent for the monofluorination of unactivated sp^3 C-H bonds of aliphatic, benzylic, and allylic containing compounds in conjunction with earth-abundant, inexpensive transition metals and commercially available photocatalysts. The use of Selectfluor in the α,α-difluorination of acid chloride derivatives and photocatalyzed ring opening-β-fluorination of cyclopropanols is

likewise discussed. Mechanistic evidence suggests the involvement of putative carbon-centered radicals (or radical ions) during fluorination with Selectfluor acting as a versatile fluorine atom transfer reagent.

Adviser: Professor Thomas Lectka

Readers: Professor Gary H. Posner

Professor Christopher Falzone

FOR MY FAMILY & FRIENDS

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PUBLICATIONS DRAWING UPON THIS DISSERTATION

(1) Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T. “A Site-Selective Approach to β-Fluorination: Photocatalyzed Ring Opening of Cyclopropanols. *Angew. Chem.* **2015,** *submitted*

(2) Bloom, S.; McCann, M.; Lectka, T. "Photocatalyzed Benzylic Fluorination: Shedding “Light” on the Involvement of Electron Transfer" *Org. Lett.* **2014,** *16*, 6338-6341.

(3) Griswold, A.; Bloom, S.; Lectka, T. "A Chelating Nucleophile Plays a Starring Role: 1, 8- Naphthyridine- Catalyzed Polycomponent α,α-Difluorination of Acid Chlorides" *J. Org. Chem.* **2014**, *79*, 9830-9834.

(4) Bloom, S.; Knippel, J. L.; Holl, M. G.; Barber, R.; Lectka, T. "A cooperative allylic fluorination: combination of nucleophilic and electrophilic fluorine sources" *Tetrahedron Lett.* **2014**, *55*, 4576-4580.

(5) Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. "Direct, Catalytic Monofluorination of sp^3 C-H Bonds: A Radical- Based Mechanism with Ionic Selectivity" *J. Am. Chem. Soc.* **2014**, *136*, 9780-9791

(6) Bloom, S.; Knippel, J. L.; Lectka, T. "A photocatalyzed aliphatic fluorination" *Chem. Sci.* **2014**, *5*, 1175-1178.

(7) Bloom, S.; Sharber, S. A.; Holl, M. G.; Knippel, J. L.; Lectka, T. "Metal-Catalyzed Benzylic Fluorination as a Synthetic Equivalent to 1, 4-Conjugate Addition of Fluoride" *J. Org. Chem.* **2013**, *78*, 11082-11086.

(8) Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. "Iron(II)-Catalyzed Benzylic Fluorination" *Org. Lett.* **2013**, *15*, 1722-1724**.**

(9) Bloom, S.; Pitts, C. R.; Miller, D.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. "A Polycomponent Metal-Catalyzed Aliphatic, Allylic, and Benzylic Fluorination" *Angew. Chem. Int. Ed.* **2012**, *51*, 10580-10583**.**

(10) Bloom, S.; Scerba, M. T.; Erb, J.; Lectka, T. "Tricomponent Catalytic α,α-difluorination of Acid Chlorides" *Org. Lett.* **2011**, *13*, 5068-5071.

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CHAPTER 1

INTRODUCTION

1.1) INTRODUCTION TO ORGANOFLUORINE CHEMISTRY

Since Henri Moissan's isolation of molecular fluorine in 1886,[1] organic chemists have sought to harvest the properties of this versatile and quite often reactive element.[2] Although today characterized as a field of great significance, organofluorine chemistry has arguably witnessed a slow growth, a considerable portion of technological advances only coming over the last 80 years.[3] From the development of Freons for the purpose of refrigeration in the 1930s,[4] evolving through its reticent role within the Manhattan project,[5] before transpiring into a multifarious field encompassing a broad spectrum of technologies, including, among others, fluoropolymers,[6] pharmaceutical/agrochemical products,[7] and

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[1] (a) Banks, R. E. *J. Fluorine Chem*. **1986,** *33*, 3-26. (b) Hamilton, J. M. Jr. *Adv. Fluorine Chem.*
[2] Hatchinson, J.; Sandford, G. *Top. Curr. Chem*. **1997,** *193*, 1-43.
[3] For a comprehensive review on the history of organofluorine chemistry see: (a) Okazoe, T. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci*. **2009,** *85*, 276-289. (b) Hudlicky, M.; Pavlath, A. *Chemistry of Organic Fluorine Compounds: A Critical Review*. Oxford University Press, **1995**.
[4] (a) Sheppard, W. A.; Sharts, C. M. *Classical methods of fluorination. In* Organic Fluorine Chemistry. W. A. Benjamin Inc.; New York, **1969,** 78-79. (b) Daudt, H. W. *Organic fluorine compound.* U. S. Patent 2005706.
[5] Goldwhite, H. *J. Fluorine Chem*. **1986,** *33*, 109-132.
[6] (a) Punkett, R. J. *Tetrafluoroethylene polymers*. U. S. Patent 2230654. (b) Locke, H. G.; Brode, W. R.; Henner, A. L. *J. Am. Chem. Soc*. **1934,** *56*, 1726-1728.
[7] (a) Hiyama, T. *Biologically active organofluorine compounds. In* Organofluorine Compounds, Chemistry and Applications. Springer, Berlin, **2000,** 137-182. (b) Filler, R.; Kobayashi, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*. Elsevier, Amsterdam, **1993**.

material science.[8] What is more, the innate synthetic challenges that it presents combined with its unique structure/reactivity relationships have made fluorine chemistry an area of fundamental interest.[9] As such, significant contributions have derived from an uncommon mix of academic and industrial scientist. Together, these faculties have *reinvented* the field, furnishing new products, processes, and instrumentation, for studying and preparing organofluorine compounds.[10] In turn, these endeavors have made research in organofluorine chemistry a topic not simply limited to a select few, but a global discipline available to the masses. Indeed, despite its inauspicious start, fluorine chemistry appears to be blossoming into a timely area of research.

1.2) PROPERTIES OF FLUORINE

Generally, efforts to prepare organofluorine compounds stem from the unique properties of the fluorine atom. Fluorine is a small atom, with an atomic radius intermediate between that of hydrogen and oxygen (1.47Å vs. 1.20Å in hydrogen and 1.52 Å in oxygen).[11] The small size of the fluorine atom makes it an ideal replacement for hydrogen atoms without dramatically affecting the overall

[8] Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, *J. Chem. Soc. Rev*. **2011,** *40*, 3496-3508.
[9] Banks, R. E. *Fluorine Chemistry at the Millennium: Fascinated by Fluorine*. Elsevier Science, **2000**.
[10] Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed*. **2013,** *52*, 8214-8264.
[11] Smith, M. B.; March, J. *March's Advanced Organic Chmistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley-Interscience: New York, USA, **2001**.

molecular size.[12] In addition to its auspicious size, fluorine is the most electronegative element in the periodic table, 3.98 on the Pauling scale. Consequently, the C-F bond is highly polarized and in this sense, is a dramatic change from a C-H bond.[13] In the polarized C-F bond, the fluorine atom bears a partial negative charge while the carbon atom bears a partial positive charge. The large columbic attraction between these charges confers significant ionic character onto the C-F bond, and as such, creates a very short and strong bond (113 kcal/mol). Another consequence of the polarized nature of the C-F bond is the presence of a low-energy σ* anti-bonding orbital. This vacant orbital is able to accept electron density from nearby electron-donating groups, such as lone pairs or σ-bonds. However, because of fluorine's high electronegativity, these interactions are regarded as weak; the three lone pairs of fluorine are held tightly to the nucleus and unable to participate as H-bond acceptors to any significant extent. This picture suggests that the C-F bond should interact with its environment through electrostatic (dipole-dipole and charge-dipole) interactions. Such interactions can indeed be observed in an intermolecular sense, where, for example, fluorine atoms orient toward the partial positive charge of an amide carbon or acidic hydrogen as well as intramolecularly.[14] Electrostatic interactions that occur within the organofluorine molecule are often substantially stronger.[13,14]

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[12] Meanwell, N. A. *J. Med. Chem*. **2011,** *54*, 2529-2591.
[13] (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, **2004**. (b) O'Hagan, D. *Chem. Soc. Rev*. **2008,** *37*, 308-319.
[14] (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007,** *317*, 1881-1886. (b) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004,** *5,* 637-643.

These properties are used to exploit the C-F bond as a predictable tool for controlling the shape of highly functional molecules.

1.3) MEDICINAL APPLICATIONS OF ORGANOFLUORINE COMPOUNDS

It is no surprise that fluorine is often pharmaceutically advantageous. A drug will bind its protein target with maximal affinity if it is conformationally pre-set into the proper orientation prior to binding. As alluded to earlier, this mode of activation can be achieved in many cases by the judicious incorporation of fluorine atoms into the backbone of the drug.[15] As a notable example, this concept was highlighted in the structure-activity relationship studies of Indinavir, an HIV protease inhibitor. In this case, the diastereomeric fluorinated analogue was found to be 14-fold less potent, a finding attributed to the interaction between the fluorine atom and β-ketone, disrupting the bioactive extended chain conformation.[16] On the other hand, conformational effects attributed to the incorporation of fluorine in alkoxylphenyl substituents have led to the discovery of these molecules as promising inhibitors of cholesteryl ester transfer protein, of considerable value for the treatment of coronary heart disease (Figure 1.1).[17]

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[15] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008,** *37*, 320-330.
[16] (a) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc*. **2001,** *123*, 7207-7219. (b) Chen, Z.; Li, Y.; Chen, E.; Hall, D. L.; Drake, P. L.; Culberson, C.; Shafer, J.; Kuo, L. C*. J. Biol. Chem*. **1994,** *269*, 26344-26348.
[17] Massa, M. A.; Spangler, D. P.; Durley, R. C.; Hickory, B. S.; Connolly, D. T.; Witherbee, B. J.; Smith, M. E.; Sikorski, J. A. *Bioorg. Med. Chem. Lett*. **2001,** *11*, 1625-1628.

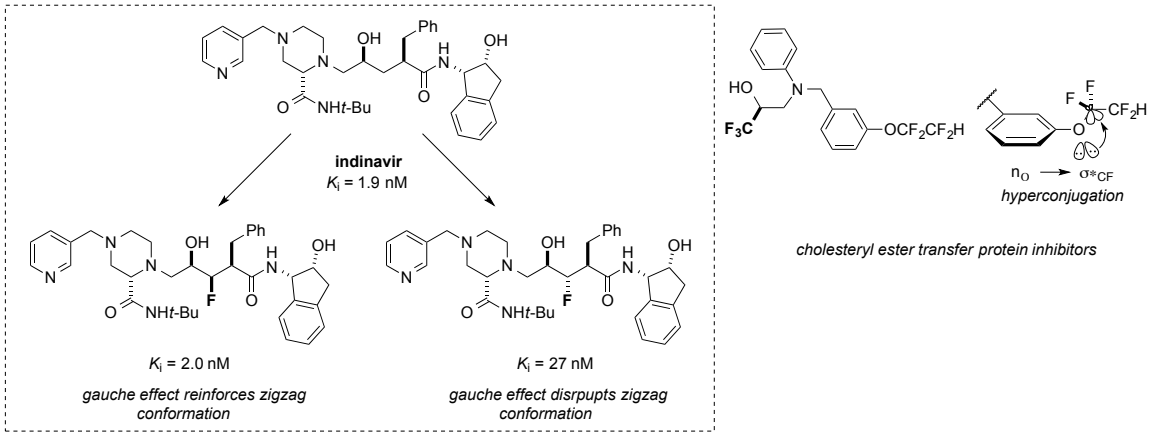


Figure 1.1. Structure/Activity of fluorine in native pharmaceuticals

In most cases, the effects of fluorine substitution at labile C-H positions resemble the latter, serving as an prominent strategy for 1) extending the half-life of potential drug candidates by heightening resistance to oxidative metabolism (esp. cytochrome P450) or blocking racemization at a chiral center 2) improving bioavailability as fluorine can increase the acidity of a proximal carboxylic acid and decrease the basicity of an amine, and 3) elevating hydrolytic stability as fluorine is known to be largely hydrophobic.[13,18] These findings have undoubtedly elicited a paradigm shift in the approach of the medicinal chemist.[19] Although there were no fluorinated drugs on the market in the early 1950s, nearly a quarter of the pharmaceuticals on the market today contain fluorine (e.g. Prozac, Celebrex, Efudex, Fludrocortisone, and Lipitor – see Figure 1.2).[15] Accordingly, selectively fluorinated compounds are nearly ubiquitous in medicinal chemistry (in addition to agrochemistry, materials, and other fields).

[18] Ismail, F. *J. Fluorine Chem.* **2002,** *118*, 27-33.
[19] Fried, J.; Subo, E. F. *J. Am. Chem. Soc.* **1954,** *76*, 1455-1456.

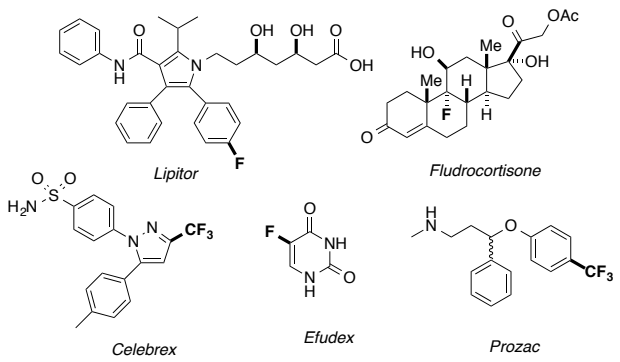


Figure 1.2. Common fluorine containing pharmaceuticals

1.4) SYNTHESIS OF ORGANOFLUORINE COMPOUNDS

Admittedly, the effect of fluorine substitution is difficult to predict. In order to solve the immediate problem of guesswork, the ability to prepare fluorinated analogues directly in the laboratory is highly valuable, allowing for more direct, and expedient testing. To meet this demand, synthetic methods, versatile reagents, and a practical means by which to study and characterize fluorinated compounds are of the essence. In particular, synthetic methods for the regio- and chemoselective incorporation of fluorine atoms into the native molecule are desirable. In this manner, a single C-H bond in the parent molecule is predictively exchanged for a C-F bond, improving both atom and cost efficiency, as no intermediates are necessary. Unfortunately, the task of introducing fluorine into organic molecules has presented a venerable challenge to synthetic chemists.[10] Early attempts often involved the direct reaction of elemental fluorine

with saturated or unsaturated systems.[20] These reactions were found to yield perfluorinated derivatives.[2] To this end, milder alternatives for oxidative fluorination were pursued. These efforts led to the introduction of transition metal fluorides (NiF_3/NiF_4, and CoF_3) as attractive reagents for fluorination.[21] However, like their predecessors, these compounds resulted in polyfluorinated adducts. Today, transition metal fluorides, NiF_3/NiF_4 (Simons Cell)[22] and CoF_3 (Fowler process)[23] are used to accomplish perfluorination on an industrial scale. These processes rely on the controlled formation of radical and cation-based intermediates as well as favorable electrochemical reactions. While futile in the way of selective monofluorination, these pioneering methods served to unveil two common modes of fluorine reactivity, nucleophilic (F^-) and electrophilic (F^+). These modes have since been used as promising strategies for directing fluorination within functional molecules. Nucleophilic fluorination, as the name suggests, involves the use of fluoride anions. Although the fluoride ion is the least nucleophilic of the halides it can affect the displacement of aryl chlorides (Halex reaction) in high boiling aprotic solvents resulting in aryl fluorides.[24] Similarly, antimony or silver based fluorides,[25] and Olah's reagent (H-F

[20] Flahaut, J.; Viel, C. *J. Fluorine Chem*. **1986,** *33*, 27-43.
[21] (a) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry*, ed. Plenum Press, **1994,** ch. 5, 121 and references cited therein. (b) Banks, R. E. ; Tatlow, J. C*. Fluorine in the First Hundred Years*, ed. Elsevier, **1986,** 267, 337 and references cited therein
[22] Simons, J. H.; Harland, W. J. *J. Electrochem. Soc.* **1949,** *95*, 47-66.
[23] Fowler, R. D.; Burford, W. B., III; Hamilton, J. M., Jr; Sweet, R. G.; Weber, C. E.; Kasper, J. S.; Litant, I. *Ind. Eng. Chem.* **1947,** *39*, 292-298.
[24] Langlois, B.; Gilbert, L.; Forat, G. *Industrial Chemistry Library* **1996,** *8*, 244-292.
[25] Tewksbury, C. I.; Haendler, H. M. *J. Am. Chem. Soc*. **1949,** *71*, 2336-2337.

Pyridine),[26] can be used to afford both aryl and allylic fluorides from the corresponding halides, triflates, phosphates, and sulfonates through nucleophilic displacement.[27] This chemistry has also led to methods for the selective mono- and difluorination of alcohols and ketones using Lewis acidic sulfur fluorides as nucleophilic fluorinating reagents.[28] Today, sulfur fluorides are used to access aliphatic monofluorides, geminal difluorides and trifluoromethyl groups through deoxyfluorination, and have become the golden standard upon which all nucleophilic fluorinating reagents are compared.[29] Despite advances in nucleophilic fluorination reagents, complementary reagents for electrophilic fluorination are underdeveloped. Initially, molecular fluorine was the only source for electrophilic fluorinations, but because of the ease of F^- formation and the dangerous properties of F_2 (highly toxic, strong oxidant), the introduction of safer, milder, and more selective sources of electrophilic fluorine was crucial. These needs spawned the development of fluoroxytrifluoromethane (CF_3OF) by Barton et al.[30] followed by others including perchloryl fluoride ($FClO_3$),[31] xenon difluoride (XeF_2),[32] nitrogen oxide fluorides (ONF),[33] and several other hypofluorides

[26] Olah, G. A. *J. Fluorine Chem*. **1986,** *33*, 377-396.
[27] (a) Wu, J. *Tet. Lett*. **2014,** *55*, 4289-4294. (b) Hollingwoth, C.; Gouverneur, V. *Chem. Commun*. **2012,** *48*, 2929-2942.
[28] Middleton, W. J. *J. Org. Chem*. **1975,** *40*, 574-578.
[29] Rajendra, P.; Singha, D. T.; Shreeve, J. M. *Advances in Orgaic Synthesis: DAST and Deoxofluor Mediated Nucleophilic Fluorintion Reactions of Organic Compounds*, **2014,** Bentham Science Publishers, 291-326.
[30] Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. *Chem. Commun*. **1968,** 804-806.
[31] (a) Schack, C. J.; Christe, K. O. *Inorg. Chem*. **1979,** *18*, 2619-2620. (b) Barton, D. H. R.; Ganguly, A. K.; Hesse, R. H.; Loo, S. N. Pechet, M. M. *Chem. Commun*. *1968*, 806-808.
[32] Tius, M. A. *Tetrahedron* **1995,** *51*, 6605-6634.
[33] Schmutzler, R. *Angew. Chem*. **1968,** *80*, 466-481.

(Figure 1.3).[34] Although these reagents served as suitable alternatives to fluorine gas, the desire for stable and nontoxic forms of electrophilic fluorine still remained. At the dawn of the second millennium, a new class of electrophilic fluorinating reagents emerged with the general structure R_2N-F or R_3N^+-F. Despite their brief history, these reagents have already gained popularity within the synthetic community.[35] More often than not, these compounds are as reactive as established electrophilic reagents, while able to offer a degree of selectivity that was previously unattainable.

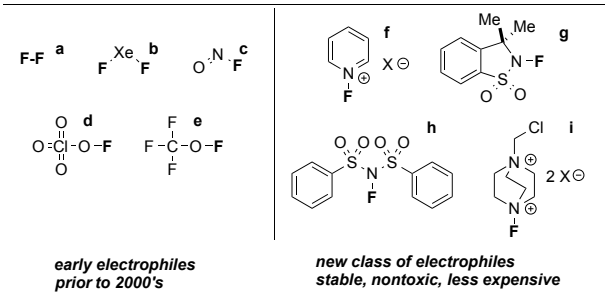


Figure 1.3. Survey of electrophilic fluorinating reagents throughout history

Among this novel class of compounds, Selectfluor (**i**) [36] has gained appreciable notoriety, being both commercially available, (one major drawback of electrophilic fluorinating reagents), and possessing desirable physical properties (stable solid, non-hydroscopic), lending itself to large-scale synthesis. Since its

[34] (a) Navarrini, W.; Tortelli, V.; Russo, A.; Corti, S. *J. Fluorine Chem*. **1999,** *95*, 27-39. (b) Rozen, S. *Chem. Rev*. **1996,** *96*, 1717-1736.
[35] (a) Zupan, M.; Stavber, S. *Trends Org. Chem*. **1995,** *5*, 11-36. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev*. **1996,** *96*, 1737-1756.
[36] Banks, R. E.; Besheesh, M. K.; Mohialdin,-Khaffaf, S. N.; Sharif, I. *J. Chem. Soc. Perkin. Trans. 1* **1996,** 2069-2076.

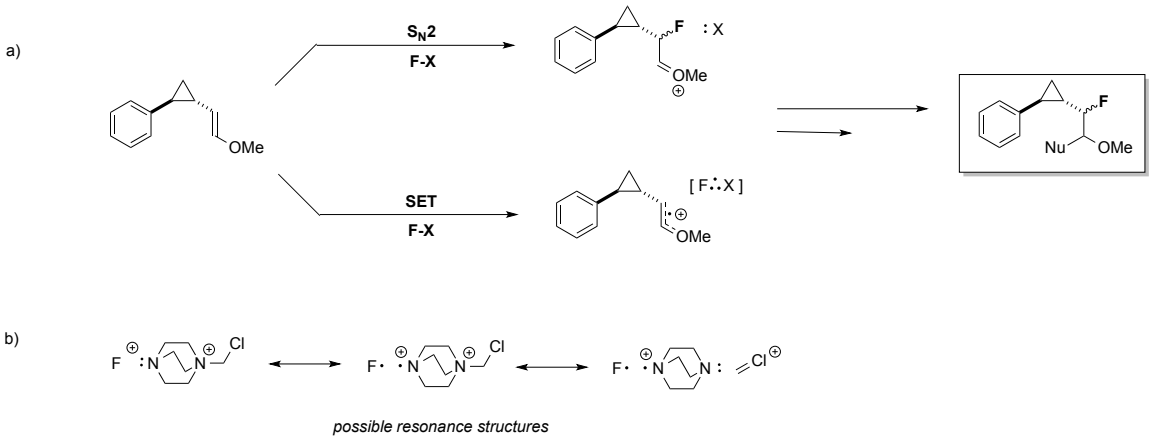
debut, countless reviews and scientific papers have surfaced highlighting the versatile reactivity of Selectfluor.[37] To this end, Selectfluor has been shown to be an affective reagent for the α-fluorination of carbonyl compounds and thioethers,[38] as well as the fluorination of aromatic rings,[36] alkenes,[39] and indoles.[40] In addition to its ability to fluorinate a wide range of potential substrates, Selectfluor can serve as a suitable oxidant. In this respect, Selectfluor has been shown to be an effective reagent for the oxidation of benzylic alcohols,[41] tertiary carbon centers,[42] and to a lesser extent, aldehydes.[43]

The widespread applications of Selectfluor and similar *N*-F reagents have prompted much interest into their mechanism of action. Currently, two possible mechanistic pathways exist: single-electron transfer (SET) or nucleophilic S_N2 substitution (these pathways are possible given the unique electronic structure of Selectfluor-Scheme 1.1 b).[36,41] In a classical S_N2 process, fluorine transfer results from direct nucleophilic attack at the fluorine atom. In opposition, in a single electron transfer (SET) process, a charge transfer complex is formed between the organic substrate and Selectfluor resulting in the loss of an electron from the substrate to Selectfluor. This pathway is characterized by the formation of discrete radical ions. Unfortunately, as shown in Scheme 1.1 a, both SET and

[37] (a) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. V.; Wong, C.-H. *Angew. Chem. Int. Ed*. **2005,** *44*, 192-212. (b) Stavber, S. *Molecules*, **2011,** *16*, 6432-6464.
[38] Lal, G. S. *J. Org. Chem*. **1993,** *58*, 2791-2796.
[39] Stavber, S.; Sotler, T.; Zupan, M. *Tetrahedron Lett*. **1994,** *35*, 1105-1108.
[40] Takeuchi, Y.; Tarui, T.; Shibata, N. *Org. Lett*. **2000,** *2*, 639-642.
[41] Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *Synlett* **1994,** 831-832.
[42] Banks, R. E.; Lawrence, N. J.; Besheesh, M. K.; Popplewell, A. L.; Pritchard, R. G. *Chem. Commun*. **1996,** 1629-1630.
[43] Liu, J.; Wong, C.-H. *Tetrahedron Lett.* **2002,** *43*, 3915-3919.

S_N2 pathways with Selectfluor often lead to the same product (even in molecules used to discern between radical or electrophilic processes such as cyclopropanes).[44] Therefore, despite compelling arguments by either side, the limits of conventional methods to study these reactions have to this point inhibited a definitive mechanism.[44]

Scheme 1.1. a) Mechanistic convergence of S_N2 and SET pathways in fluorination reactions with Selectfluor. b) Resonance contributers in the reactivity of Selectfluor



Provided the versatile nature of Selectfluor, we gathered its application to chemical synthesis and catalysis, especially in the way of forming new C-F bonds, could be of value to study. Herein, the use of Selectfluor as a site-selective fluorinating reagent for the direct, monofluorination of aliphatic, benzylic, and allylic compounds as well as the difluorination of acid chlorides and ring

[44] Vincent, S. P.; Burkart, M. D.; C.-Y., Tsai, Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999,** *64*, 5264-5279.

opening-β-fluorination of cyclopropanols is reported. These reactions are catalyzed, or in some cases promoted by the incorporation of redox active transition metals or commercial photocatalysts.

CHAPTER 2

TRICOMPONENT CATALYTIC α,α-DIFLUORINATION OF ACID CHLORIDES

2.1) α-FLUORINATION OF CARBONYL-CONTAINING COMPOUNDS

Strategic fluorination has become an ever more important weapon in the armamentarium of medicinal chemistry.[45] Substitution of drug molecules with fluorine has been shown to affect the activity of the drug *in vivo*.[46] As a result, the inclusion of fluorine into a host of organic substrates has resulted in a large number of viable drug candidates for the treatment of disease.[45,46] In many cases, fluorine is chosen to replace hydrogen at metabolically labile sites in a biologically active molecule.[47] Along these lines, the positions α to a carbonyl group are often targeted for fluorination.[47] Some time ago, our group reported on the enantioselective α-fluorination of ketene enolates. This synthetic triumph in the way of enatioselective fluorination reactions was used to access both simple and pharmaceutically adventitious, optically enriched α-fluorinated carboxylic acid derivatives directly from commercially available acid chlorides (**1**). What is more, this chemistry showcased the synthetic versatility of a "Trifucntional"

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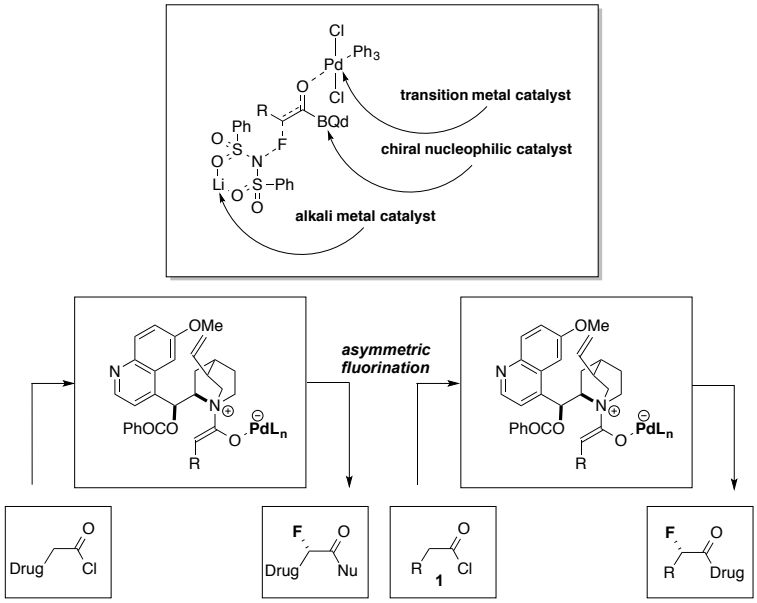
[45] (a) Liu, P.; Sharon, A.; Chu, C. K. *J. Fluorine Chem*. **2008,** *129*, 743–766. (b) Park, B. K.; Kitteringham, N. R. *Drug Metab. Rev*. **1994,** *26*, 605–643. (c) Smart, B. E. *J. Fluorine Chem*. **2001,** *109*, 3–11. (d) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., **2009.** (e) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, **1973**.

[46] Park, K. B.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol*. **2001,** *41*, 443–70.

[47] Cahard, D.; Xu, X.; Couve-Bonaire, S.; Pannecoucke, X. *Chem. Soc. Rev*. **2010,** *39*, 558–568.

platform, in which a chiral nucleophile, benzoylquinidine (BQd), a transition metal-based Lewis acid cocatalyst, $(PPh_3)PdCl_2$, and alkali metal salt, lithium perchlorate, work synergistically to afford metal-coordinated, chiral ketene enolates (Scheme 2.1).

Scheme 2.1. Polycomponent catalysis for the enantioselective α-fluorination of acid chlorides



Interestingly, we found that α,α-difluorinated products were not observed under our reaction conditions even in the presence of excess *N*-fluorobenzenesulfonamide, our active fluorinating reagent. As selective difluorination α to a carbonyl is a synthetic challenge that has yet to be effectively overcome, we decided to pursue this active and timely area of research. Unfortunately, monocarbonyl compounds have proven to be very difficult

substrates for difluorination.[48] In this sense, highly acidic compounds including 1,3-diketones and β-ketoesters are often targeted as substrates for difluorination employing Selectfluor,[49] *N*-fluoro pyridinium salts,[50] and *N*-fluorosulphonimides.[51] Additionally, electrochemical methods have gained popularity among techniques for accessing a variety of α-fluorinated products.[52] Although notable, such efforts provide unsatisfactory mixtures of mono- and difluorinated adducts. On the other hand, monocarbonyl enolates have been shown to undergo selective mono- and difluorination in the presence of an *N*-F-sultam.[53] However, these methods are generally limited in substrate scope and their need for noncommercial sources of electrophilic fluorine.

2.2) TRICOMPONENT METHODOLGY

Instead, we envisaged the use of acid chlorides (**1**) as ideal substrates for one-pot, selective difluorination. They are inexpensive, readily available, and their α-positions are suitably acidic. To this end, we identified a unique "tricomponent" catalytic system for α,α-difluorination that involves a main group Lewis acid

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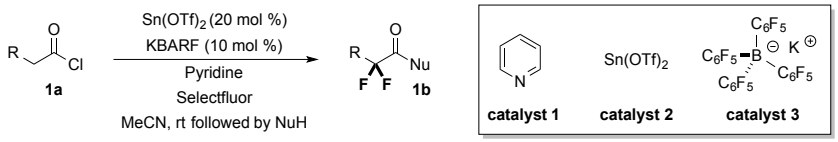
[48] (a) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002,** *17*, 2609– 2615. (b) Tsushima, T.; Kawada, K.; Tsuji, T. *J. Org. Chem*. **1982,** *47*, 1107–1110.
[49] (a) Stavber, G.; Stavber, S. *Adv. Synth. Catal*. **2010,** *352*, 2838–2846. (b) Xiao, J.-C.; Shreeve, J. M. *J. Fluorine Chem*. **2005,** *126*, 475–478. (c) Stavber, G.; Zupan, M.; Jereb, M.; Stavber, S. *Org. Lett.* **2004,** *6*, 4973–4976.
[50] (a) Umemoto, T.; Tomita, K.; Kawada, K.; Tomizawa, G. EPA 0204535 (Priority 3.6.85). (b) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990,** *112*, 8563–8575.
[51] Xu, Z.-Q.; DesMarteau, D. D.; Gotoh, Y. *J. Chem. Soc., Chem. Commun*. **1991,** 179–181.
[52] (a) Laurent, E.; Marquet, B.; Tardivel, R. *Tetrahedron* **1989,** *45*, 4431–4444. (b) Laurent, E.; Marquet, B.; Tardivel, R.; Thiebault, H. *Tetrahedron Lett*. **1987,** *28*, 2359–2362.
[53] Differding, E.; Ruegg, G. M.; Lang, R. *Tetrahedron Lett*. **1991,** *32*, 1779–1782.

($Sn(OTf)_2$), a catalytic nucleophile that also serves as a reagent (pyridine), and an anionic phase transfer catalyst (KBARF) [54] (potassium tetrakis-(pentafluorophenyl)borate). These three catalysts work synergistically to effect the efficient α,α-difluorination (**2**) of a variety of acid chlorides employing Selectfluor (1-chloromethyl-4-fluoro-1,4- diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[37, 55] as an electrophilic fluorinating agent and MeCN as solvent (Scheme 2.2)

Scheme 2.2. Tricomponent catalytic system for α,α-difluorination

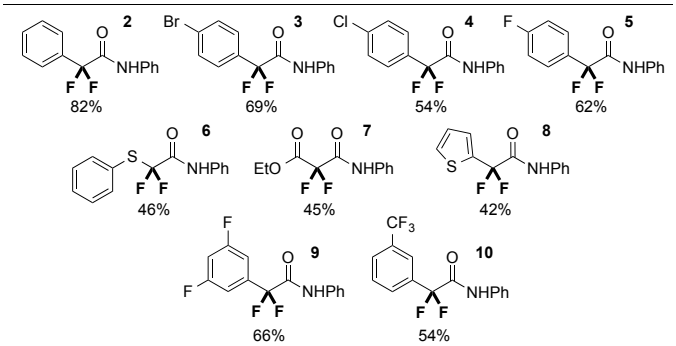


This new method illustrates the power of catalysts acting cooperatively to produce a positive outcome; in this case, the combination of three catalysts is especially notable. No reaction occurs in the absence of pyridine (nucleophilic catalyst and dehydrohalogenating agent), and yields are substantially diminished without tin(II) triflate (Lewis acid catalyst). It is also important to note that selective difluorination cannot be obtained using other tertiary amines as a base or with other Lewis acid co-catalyst to the extent of that with tin. One of the most notable limitations on the use of Selectfluor in many fluorination reactions,

[54] For a review of fluorinated tetraarylborates as anionic phasetransfer catalysts, see: Ichikawa, J.; Kobayashi, H.; Sonada, T. *Rep. Inst. Adv. Mater. Study* **1988,** *2*, 189–207.
[55] For a review of Selectfluor, see: Wong, C.-H. *Angew. Chem., Int. Ed.* **2005,** *44*, 192–212.

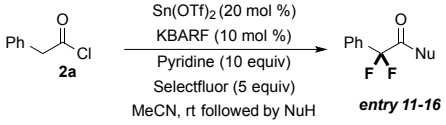
including our own, is its relative insolubility in commonly used organic solvents. Even in MeCN, the solvent of choice for many reactions with Selectfluor, its solubility is undesirably low and presents a limitation in its overall use as a fluorinating agent.[55] In our reaction, increased ratios of difluorinated product were achieved utilizing a minimal amount of solvent; however, substantial quantities of ketene dimer were likewise prevalent. To minimize dimer formation, lower reaction temperatures and slower addition times of acid chloride were examined. Unfortunately, these attempts resulted in unsatisfactory yields of difluorinated product. At this point, we sought a means to increase Selectfluor solubility namely, we imagined that the addition of an anionic phase transfer catalyst (anionic-PTC) could act to bring Selectfluor into solution more effectively. Consequently, we screened KBARF[52] as a third catalyst and found a significant increase in reaction rate, cleanliness, and yield; the role of the KBARF co-catalyst is therefore suggestive of a solubilizing agent for Selectfluor. In the present method, it is apparent that the anionic-PTC is unlikely to engage detrimentally with the Lewis acid $Sn(OTf)_2$ and pyridine and, thus, makes an ideal complement to the polycatalytic system.

Table 2.1. Survey of α,α-difluorinated products



Using our optimized conditions, this reaction was found to afford a survey of aromatic and heteroaromatic difluorinated amides employing aniline as a quenching agent (Table 2.1). Unfortunately, substitution of the aromatic ring with electron-rich substituents was found to give unsatisfactory yields of difluorinated product (as opposed to more electron-deficient aromatics). Upon further analysis, steric effects were also found to influence the selectivity of difluorination. Substrates possessing bulky substituents near the α-center afforded predominantly monofluorinated products, and those whose α-protons lack significant acidity were likewise found to be ineffective candidates for difluorination. Despite such limitations, this reaction does provide accessibility to a host of carboxylic acid derivatives through selection of different quenching agents (Table 2.2). This in turn allows for a high degree of variability in the functional group of the difluorinated product, thereby eliminating the need for prefunctionalized substrates.

Table 2.2. Derivitization of acid chlorides through nucleophilic quenching



entry	NuH	yield %
11	EtOH	71
12	$NaBH_4$	73
13	MeOH	79
14	H_2O	60
15	BnOH	74
16	$HNEt_2$	63

2.3) CONCLUDING REMARKS

While the fluorination of carbonyl compounds using metal enolates and Selectfluor has generally yielded monofluorinated products, the use of acid chlorides, being susceptible to sequential enolization, have proven effective substrates for difluorination in combination with an operationally straightforward tricomponent catalyst system.

CHAPTER 3

A CHELATING NUCLEOPHILE PLAYS A STARRING ROLE: 1,8-NAPHTHYRIDINE-CATALYZED POLYCOMPONENT α,α-DIFLUORINATION OF ACID CHLORIDES

3.1) INTRODUCTION TO CHELATING NUCLEOPHILES

It is known that organic nucleophiles can be combined with Lewis acids to generate dually activated enolates that enhance thermal stability and help introduce stereochemical control.[56,57] In this area, Lewis acid assisted chelate organization has proven to be a particularly useful tool in asymmetric halogenation reactions.[58] i.e. the stereoselective α-fluorination of β-ketoesters with titanium,[59] palladium,[60] and copper[61] catalysts. While monofluorination through Lewis acid chelated intermediates has been extensively studied, use of chelated nucleophiles for fluorination remains uncharted.

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[56] (a) Erb, J.; Paull, D. H.; Belding, L.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc*. **2011,** *133*, 7536–7546. (b) Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T. *J. Am. Chem. Soc*. **2008,** *130*, 17260–17261. (c) Stegbauer, L.; Sladojevich, F.; Dixon, D. *Chem. Sci*. **2012,** *3*, 942–958.

[57] (a) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed*. **1999,** *38*, 1468–1470. (b) Evans, D.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc*. **2001,** *123*, 10840–10852.

[58] Smith, A. R.; Hii, K. K. *Chem. Rev.* **2011,** *111,* 1637–1656.

[59] Hintermann, L.; Togni, A. *Angew. Chem*. **2000,** *112*, 4530–4533.

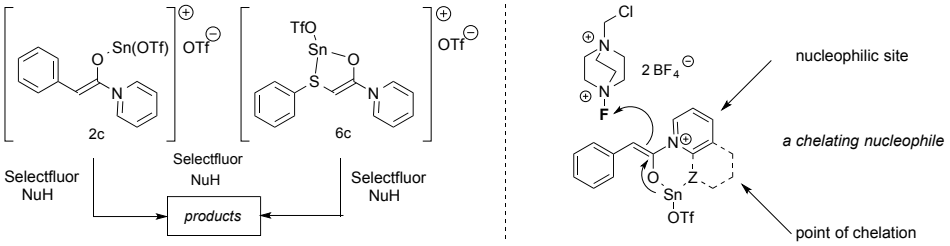
[60] Lectard, S.; Hamashima, Y.; Sodeoka, M. *Adv. Synth. Catal*. **2010,** *352*, 2708.

[61] Ma, J. A.; Cahard, D. *Tetrahedron: Asymmetry* **2004,** *15*, 1007– 1011.

3.2) TRICOMPONENT METHODOLGY

In our previous investigation into the difluorination of acid chlorides, we discovered a tricomponent catalytic system utilizing a Lewis acid, $Sn(OTf)_2$, a nucleophilic base (pyridine), and an anionic phase transfer catalyst, $KB(C_6H_6)_4$, to effect the selective α,α-difluorination of a series of acid chlorides in the presence of Selectfluor.[62] Although notable, this methodology was very limited to extensively acidified, electron deficient aromatics, and α-dicarbonyl compounds. Perhaps more interesting, in the course of our studies, we noted that a sulfur containing compound **6** underwent difluorination more readily than the oxygen and nitrogen counterpart. At the time, we reasoned that this effect could not solely be attributed to the increased acidity at the α-position; instead, it was postulated that sulfur may coordinate to the tin catalyst to form an internal chelate along with the carbonyl (Figure 3.1, **6c**).

Scheme 3.1. Proposed tin enolate intermediates derived from acid chloride substrates



[62] Bloom, S.; Scerba, M. T.; Erb, J.; Lectka, T. *Org. Lett.* **2011,** *13*, 5068–5071.

Accordingly, we gathered that the incorporation of a structurally simple molecule that could provide both a point of chelation and a nucleophilic site might prove advantageous, simultaneously generating the ketene enolate and binding the tin catalyst (Scheme 3.1). Initially, we screened cyclic amidine derivatives, as they have been shown to operate as efficient *N*-acylation catalysts.[63] Bicyclic isothioureas were found to provide relatively low conversion rates for the difluorination of 2-naphthylacetyl chloride, a compound which does not difluorinate under our tricomponent reaction conditions (Table 3.1). From this finding, we considered using other amidine catalysts possessing a fused bicyclic core. Naphthyridines, a class of compounds consisting of two fused pyridine rings, are emblematic of such a system. 1,8-naphthyridines are present in the antimicrobials nalidixic acid and gemifloxacin and have been employed in drug candidates for the treatment of Alzheimer's disease.[64,65] Traditionally, 1,8-naphthyridine is used as a versatile ligand with monodentate and bidentate bridging capacities and is known for the formation of weak chelates with single metal centers that possess small bite angles.[66] When we employed a catalytic amount of 1,8-naphthyridine in the test reaction, we found it was compatible with Selectfluor, unlike other nucleophilic sources (such as DMAP) and were rewarded with a considerable increase in both yield and selectivity. Other heterocyclic isomers, on the other hand (entries 7 and 8), fared less well.

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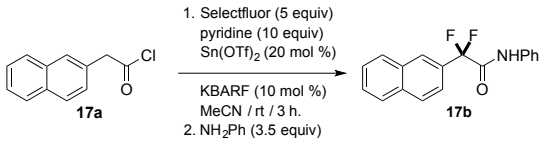
[63] Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007,** *9*, 37–40.
[64] Lowe, M. M.; Lamb, H. M. *Drugs* **2000,** *59*, 1137–1148.
[65] Egea, J.; De Los Rios, C. *Curr. Top. Med. Chem.* **2011,** *11*, 2807–2823.
[66] Suzuki, T. *Inorg. Chim. Acta.* **2006,** *359*, 2431–2438.

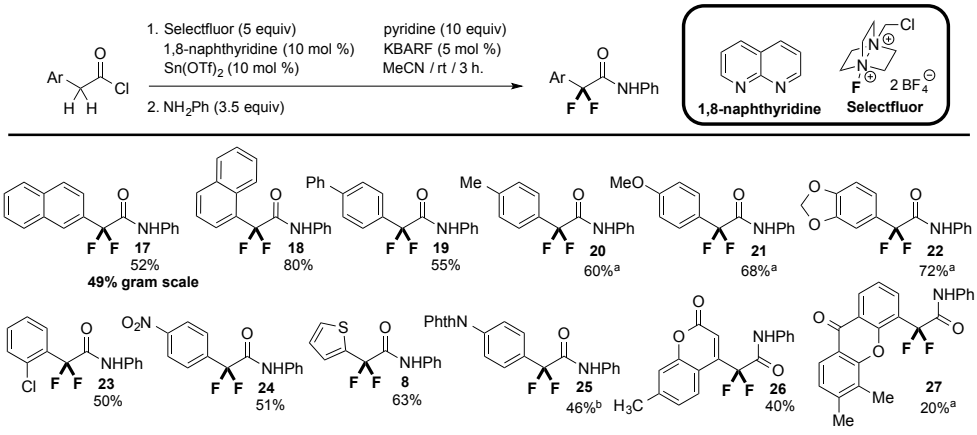
Table 3.1. Screen of chelating nucleophiles for α,α-difluorination



entry	*catalyst*	*yield %*	*entry*	*catalyst*	*yield %*
1	none	0	5		15
2		4	6		52[a]
3		5	7		6
4		11	8		28

With this catalyst in hand, a survey of difluorinated compounds were obtained in modest yield (Table 3.2). What is more, the reaction was shown (using **17**) to be scalable up to a gram or more without loss in yield. Unfortunately, the system was not conducive to aliphatic compounds; an investigation of butyryl chloride revealed minor (<10% by NMR) difluorination yields.

Table 3.2. Survey of α,α-difluorinated products



Key: (a) 50 mol % $Sn(OTf)_2$; (b) yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard due to product instability

The applicability of this system to medicinally relevant molecules was also

investigated. Phthalimide derivatives (**25**) have been used as anesthetics,[67] tumoricidals, and DNA-cleaving agents. [68] In particular, N-phthaloyl aminocarboxylic acids have been shown to have antimicrobial properties.[69] Entry **26** is an example of a coumarin, a class of bioactive molecules with reported anti-HIV, antitumor, and antiseptic properties.[70] Coumarins have also been used to treat asthma and lymphedema.[71] Vadimezan, the carboxylic acid derivative of **27**, is a tumor-vascular disrupting agent with promising phase II clinical trial results regarding the treatment of advanced non-small cell lung cancer when combined with other mitotic inhibitors.[72]

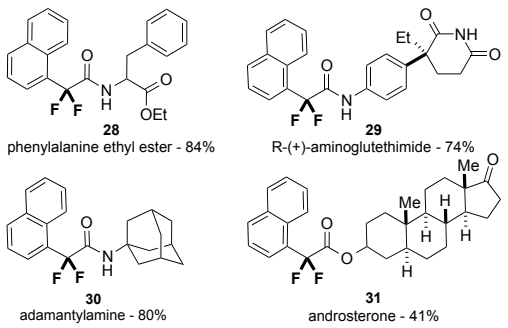


Figure 3.1. α,α-dilfuorination in natural product and pharmaceutical derivitization

Expanding upon the scope of this reaction, the combination of difluorination with natural product derivatization can yield a new class of intriguing medicinally

[67] Dasettimo, A.; Primofiore, G.; Ferrarini, P.; Ferretti, M.; Barili, P.; Tellini, N.; Bianchini, P. *Eur. J. Med. Chem.* **1989,** *24*, 263–268.
[68] Brana, M.; Ramos, A. *Curr. Med. Chem.* **2001,** *1*, 237–255.
[69] Al-Farhan, K.; Ghazzali, M.; Al-Hazimi, H.; El-Faham, A.; Reedii, J. *J. Mol. Struct.* **2011,** *994*, 269–275.
[70] Stefanova, T.; Nikolova, N.; Toshkova, R.; Neychev, H. *J. Exp. Ther. Oncol.* **2007,** *6*, 107–115.
[71] Farinola, N.; Piller, N. *Lymphatic Res. Biol.* **2005,** *3*, 81–86.
[72] Buchanan, C. M.; Shih, J. H.; Astin, J. W.; Rewcastle, G. W.; Flanagan, J. U.; Crosier, P. S.; Shepherd, P. R. *Clin. Sci.* **2012,** *122*, 449–457.

relevant compounds (Figure 3.1). As this reaction is thought to proceed through a highly reactive ketene enolate, it is also possible to quench it with a range of nucleophiles to produce various highly functionalized products.[73] Accordingly, natural product derivatization was investigated with a protected amino acid, phenylalanine ethyl ester (**28**), because of its commercial availability, high solubility in acetonitrile, and single nucleophilic site. (R)- (+)-Aminoglutethimide (**29**) was an attractive candidate because of its role in blocking the production of cholesterol-derived steroids through potent inhibition of P450scc and aromatase.[74] Adamantylamine (**30**) was another promising nucleophile as it makes up the core of memantine, a NMDA antagonist used to treat Alzheimer's disease.[75] In addition to these pharmacophores, an alcohol, the endogenous steroid hormone, androsterone (**31**), was also used as a nucleophilic quenching agent. Despite a lower yield, the difluorinated analogue was isolated in excellent selectivity.

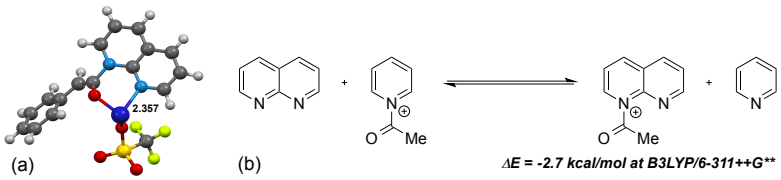
3.3) MECHANISTIC INSIGHT

In order to gain insight into the reaction mechanism and the role of the proposed chelate, IR and ^{19}F NMR studies were undertaken as no ^{119}Sn NMR signal could be obtained in the solution phase. By comparing IR frequencies, it

[73] Erb, J.; Alden-Danforth, E.; Kopf, N.; Scerba, M. T.; Lectka, T. *J. Org. Chem*. **2010,** *75*, 969–971.
[74] Siraki, A. G.; Bonini, M. G.; Jiang, J.; Ehrenshaft, M.; Mason, R. P. *Chem. Res. Toxicol*. **2007,** *20*, 1038–1045.
[75] Robinson, D. M.; Keating, G. M. *Drugs* **2006,** *66*, 1515– 1534.

was possible to probe for a coordinated intermediate. In acetonitrile, 1-naphthylacetyl chloride absorbed strongly at 1797 cm^{-1}, characteristic of acid chlorides.[76] When 1,8-naphthyridine was combined with the acid chloride, bands were observed at 1628 and 1606 cm^{-1}, indicative of an acylpyridinium salt.[77] Upon the addition of $Sn(OTf)_2$ to the naphthyridine-acid chloride mixture, a band emerged at 1736 cm^{-1}, suggesting coordination between tin and the carbonyl group.[78] Moreover, bands at 1272 and 1375 cm^{-1} imply ionic $CF_3SO_3^-$ and monodentate-bound trifluoromethanesulfonate, respectively.[79] Additionally, a peak at 482 cm^{-1} is characteristic of bonds between imino nitrogen atoms and tin.[80]

Scheme 3.2. Computational support for the formation of a chelated metal enolate



(a) B3LYP/LanL2DZ calculations for chelated tin-nitrogen bond length; and (b) B3LYP/6311^{++}G** naphthyridine-pyridine acetylation isodesmic reaction

Although these data are suggestive of a chelate, they do not provide

[76] Larkin, P. *Infrared and Raman Spectroscopy; Principles and Spectral Interpretation*; Elsevier: Waltham, **2011.**
[77] Cook, D. *Can. J. Chem.* **1962,** *40*, 2362–2368.
[78] Nieto-Alvarez, D. A.; Jimenez-Cruz, F.; Mancilla, T. *Polyhedron* **2002,** *21*, 417–420.
[79] Lawrance, G. *Chem. Rev*. **1986,** *86*, 17–33.
[80] Dey, D.; Saha, M. K.; Das, M. K.; Bhartiya, N.; Bansal, R. K.; Rosair, G.; Mitra, S. *Polyhedron* **1999,** *18*, 2687–2696.

definitive proof; a ^{19}F NMR study was therefore conducted for further validation. The ^{19}F signal of the enolizable substrate, 2-fluoro-2-phenylacetyl chloride, was carefully observed in CD_3CN over the course of a series of reaction conditions. When stoichiometric 1,8-naphthyridine was added a precipitate formed (putatively the acyl naphthyridinium salt). Following the addition of stoichiometric $Sn(OTf)_2$, a slight shift (+0.05 ppm) was also detected. To generate the enolate complex, 1 equiv of pyridine was then added and the solution became homogeneous again. This caused the sharp doublet at -161.45 to disappear and a new singlet at -123.25 ppm to emerge, which is consistent with that of analogous fluorinated silyl enolates.[81] On the basis of the IR data, a chelated enolate with a single monodentate-bound trifluoromethanesulfonate was examined computationally (Scheme 3.2); we deemed the nonfluorinated enolate most relevant as ^{19}F NMR studies indicated that the first fluorination is rate-determining. The distance between nitrogen and tin was calculated at B3LYP/LanL2DZ to be 2.36 Å, which is comparable with average tin(II)-nitrogen bonds reported to be ~2.39 Å.[82] Computations at the B3LYP/6-311++G** level of theory also revealed that naphthyridine acylation is thermodynamically favorable over that of pyridine. From this calculation, it can be reasoned that even in the presence of excess pyridine a naphthyridine-tin chelate can form *in situ*.

[81] Wang, W.; Chen, Q.; Guo, Y. *Synlett* **2011,** *18*, 2705–2708.
[82] Fricker, S. *Metal Compounds in Cancer Therapy*; Chapman & Hall: Scarborough, **1994**.

3.4) CONCLUDING REMARKS

In all, it has been demonstrated that a chelating nucleophile, 1,8-naphthyridine, successfully augments difluorination methodology to increase substrate scope and selectivity. Quenching the reaction with natural products also serves as an effective strategy for the generation of late-stage difluorinated molecules.

CHAPTER 4

A POLYCOMPONENT METAL-CATALYZED ALIPHATIC, ALLYLIC, AND BENZYLIC FLUORINATION

4.1) INTRODUCTION TO sp^3 C-H FLUORINATION

The selective incorporation of fluorine into organic molecules has advanced in dramatic ways over the last 30 years.[83] Although arene[84] and alkyne[85] fluorination using metal catalysis has received much attention, corresponding methods for metal-catalyzed alkane fluorination remain only a promising goal.[86] To date, the most notable methods for alkane fluorination[87] involve the use of stoichiometric quantities of difficult-to-handle or indiscriminate reagents such as elemental fluorine,[88] cobalt trifluoride (polyfluorination),[89] or the potentially

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[83] (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008,** *37*, 320 – 330. (b) Cahard, D.; Xu, X.; CouveBonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev*. **2010,** *39*, 558 – 568.

[84] (a) Watson, D.; Mingjuan, S.; Teverovskiy, G.; Zhang, Y.; Jorge, G. F.; Kinzel, T.; Buchwald, S. L. *Science* **2009,** *325*, 1661 – 1664. (b) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010,** 1804 – 1821. (c) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem*. **2010,** *122*, 2265 – 2268; *Angew. Chem. Int. Ed*. **2010,** *49*, 2219 – 2222. (d) Ye, Y.; Lee, S.; Sanford, M. S. *Org. Lett.* **2011,** *13*, 5464 – 5467. (e) Loy, R. N.; Sanford, M. S. *Org. Lett*. **2011,** *13*, 2548 – 2551.

[85] (a) Akana, J. A.; Bhattacharyya, K. X.; Mller, P.; Sadighi, J. P. *J. Am. Chem. Soc*. **2007,** *129*, 7736 – 7737. (b) Gorske, B. C.; Mbofana, C. T.; Miller, S. J. *Org. Lett*. **2009,** *11*, 4318 – 4321.

[86] Considerable progress has been made in aliphatic C-H bond activation; see: "C-H activation": Davies, H. M.; Dick, A. R. *Top. Curr. Chem*. **2010,** 303 – 346; and for a representative example, see: Chen, M. S.; White, M. C. *Science* **2007,** *318*, 783 – 787.

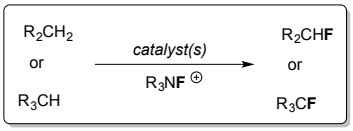
[87] Fluorination of alkane derived free radicals has been recently observed: Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquins, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012,** *134*, 4026 – 4029.

[88] (a) Miller, W. T.; Dittman, A. L. *J. Am. Chem. Soc*. **1956,** *78*, 2793 – 2797. (b) Miller, W. T.; Koch, D. D.; McLafferty, F. W. *J. Am. Chem. Soc*. **1956,** *78*, 4992 – 4995. (c) Miller, W. T.; Koch, S. D. *J. Am. Chem. Soc.* **1957,** *79*, 3084 – 3089. (d) Barton, D. H. R.; Hesse, R. H.; Markwell, R. F.; Pechet, M. M.; Toh, H. T. *J. Am. Chem. Soc*. **1976,** *98*, 3034 – 3035. (e) Rozen, S. *Acc. Chem. Res*. **1988,** *21*, 307 – 312.

[89] (a) Fowler, R. W.; Burford, W. B.; Hamilton, J. M.; Sweet, R. G.; Weber, C. E.; Kasper, J. S.; Litant, I. *Preparation, Properties and Technology of Fluorine and Organic Fluoro Compounds*,

explosive cesium fluoroxysulfate.[90] Therefore, a mild protocol involving inexpensive, and synthetically mild reagents would be highly desirable. What is more, such a method would be complementary to pioneering methods, and could prove amendable to closely related allylic and benzylic substrates.

Scheme 4.1. Direct fluorination of sp^3 C-H bonds in alkanes and similar systems



4.2) METAL CATALYZED METHODOLOGY

In the course of our difluorination chemistry involving 1,8-naphthyridine, we became particularly interested in the question of whether the α,α-difluorination of aliphatic acid chlorides could be selectively catalyzed under mild reaction conditions. Unfortunately, our optimized protocol afforded only minor amounts of difluorinated product for an aliphatic test substrate, butyryl chloride. At that time, we performed a brief screening of other transition metals to promote the difluorination reaction. While most transition metals failed to improve the reaction, often leading to undesirable products, copper(I) iodide provided a significant increase in the yield of difluorinated product. In addition to the

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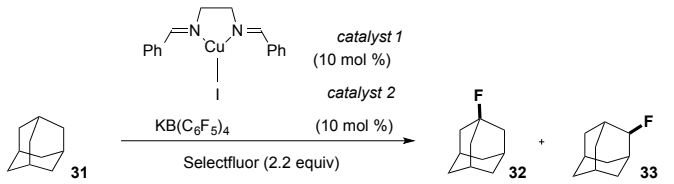
McGraw Hill, New York, **1951,** pp. 349 – 371; (b) Joyner, B. D. *J. Fluorine Chem*. **1986,** *33*, 337 – 346. (c) Burdon, J.; Creasey, J. C.; Proctor, L. D.; Plevey, R. G.; Yeoman, J. R. N. *J. Chem. Soc. Perkin Trans. 2* **1991,** 445 – 447.

[90] (a) Furin, G. G. *New Fluorinating Agents in Organic Synthesis*, Springer, Berlin, **1989,** pp. 135 – 168. (b) Zupan, M.; Stavber, S. *Tetrahedron* **1989,** *45*, 2737 – 2742.

expected α,α-dilfuorinated product, fluorination of remote, unactivated sp^3-carbon atoms along the alkyl chain were observed. This finding prompted us to examine whether the combination of a redox active transition metal and Selectfluor could be used for the selective monofluorination of alkanes, perhaps opening up a realm of fluorination catalysis in addition to the much-studied aromatic fluorination. Enticed by this potentially prosperous avenue we chose first to focus our efforts on the well-characterized adamantane system **31** and its fluorinated derivatives, **32** and **33**. Initial catalyst screening employed a variety of transition-metal salts, Selectfluor, and adamantane in dry MeCN at room temperature for 24 h (Table 4.1). Most notably, 10 mol % of CuI turned out to be a competent lead, yielding 1-fluoroadamantane (**32**) in 18 % yield and in good selectivity [8:1 with respect to 2- fluoroadamantane (**33**)]. It should be noted that in the absence of a metal catalyst, the reaction produced no fluorinated products under the specified reaction conditions. At this point, a number of other copper(I) salts were screened (CuBr, CuCl, $CuClO_4$), but CuI proved to be the most effective. For example, CuCl afforded only trace amounts of product, whereas $CuClO_4$ resulted in a complex mixture of highly fluorinated adamantane-based products in variable quantities. In an effort to increase the yield of fluorinated adamantine, screening revealed the reaction could be accelerated by the addition of both a phase-transfer catalyst, $KB(C_6F_5)_4$ (10 mol %), acting as a solubilizing agent and presumed metal counteranion exchanger for Selectfluor,[62] and by the addition of

N,N-bis(phenylmethylene)-1,2-ethanediamine (BPMED; 10 mol %) as a ligand for copper.

Table 4.1. Optimization of alkane fluorination reaction conditions for adamantane

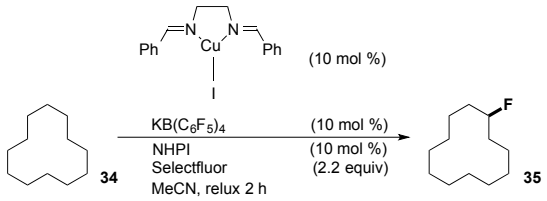


catalyst	solvent	ligand	T[ºC]	**32/33**	yield [%]
	MeCN	-	25	-	0[a,b]
CuI	MeCN	-	25	8:1	18[a,b]
CuI	MeCN	BPMED	25	7:1	28[a,b]
CuI	MeCN	BPMED	25	5:1	35[a]
CuI	MeCN	BPMED	25	-	trace
CuI	MeCN	BPMED	25	3:1	12[a]
CuI	**MeCN**	**BPMED**	**25**	**8.4:1**	**75[a]**

(a) Yield without $KB(C_6F_5)_4$. (b) MeCN was not degassed. (c) Yield after 1 h. (d) Yield after 3 h. Otherwise yields were determined after 24 h by ^{19}F NMRspectroscopy using 2-fluorobenzonitrile as an internal standard, and also by column chromatography. Final entry indicates yield of isolated product.

Unfortunately, these reaction conditions were not amenable to alkanes composed entirely of secondary, methylene carbons prompting us to re-examine our conditions. Upon further screening with a less reactive alkane, cyclododecane **34** (Table 4.2), it was found that heating of the reaction mixture with *N*-hydroxyphthalimide (10 mol %), which is known to form the phthalimide *N*-oxyl (PINO) radical *in situ* in the presence of redox active metals, along with KI (10 mol %), allowed for optimal results with most substrates.

Table 4.2. Optimization of alkane fluorination reaction conditions for cyclododecane



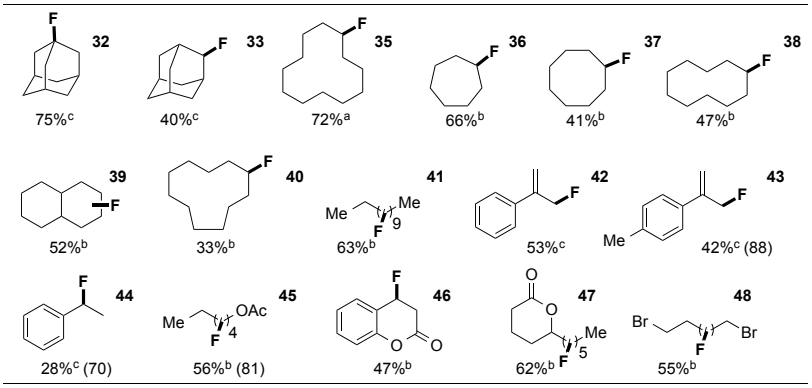
entry	catalyst	cocatalyst	cocatalyst	yield [%]
1	(BPMED)CuI	-	-	26
2	(BPMED)CuI	$KB(C_6F_5)_4$	-	44
3	(BPMED)CuI	$KB(C_6F_5)_4$	NHPI	63
4	(BPMED)CuI	$KB(C_6F_5)_4$	NHPI[b]	72

(a) All reaction were performed at reflux for 2 h and yields were determined by ^{19}F NMR spectroscopy using 3-chlorobenzotrifluoride as an internal standard and isolation of the product by chromatography. b) Reaction was performed with KI (10 mol %) as additive

However, it was found that longer reaction times were often deleterious, resulting in acetamide formation, likely through a Ritter reaction. This is an unsurprising observation given the demonstrable release of Prelog strain[91] during S_N1 reactions of 8- and 10-membered ring systems, and that reaction times in MeCN reflect the susceptibility of substrates to solvolysis. In such instances, reaction times between one and three hours were found to be satisfactory for most alkanes (Table 4.3).

[91] Goldfarb, Y. I.; Belenkii, L. I. *Russ. Chem. Rev*. **1960,** *29*, 214 – 235.

Table 4.3. Survey of fluorinated alkanes



(a) 10 mol % KI. (b) 1.2 equiv KI. (c) No KI. Yields within parentheses for entries 42-44 are based on recovered starting materials. All reactions were monitored by ^{19}F NMR spectroscopy and yields determined using 3-chlorobenzotrifluoride as an internal standard and/or isolation of the product by column chromatography.

Expanding the substrate scope, allylic compounds were found to be interesting in their own way. For example, α-methylstyrenes are known to fluorinate in MeCN to form fluoroacetamides (under so-called electrophilic conditions) admixed with variable quantities of allylic fluorides.[92] Under catalytic conditions at room temperature, as demonstrated herein, the allylic fluorides predominate to the virtual exclusion of the fluoroacetamides (compounds **42** and **43**). This result would seem to bolster the case for a different (non-electrophilic) mechanistic pathway. As another noteworthy example, a benzylic substrate, ethylbenzene, fluorinated to provide α-fluoroethylbenzene (**44**) in 28 % yield. Once again, this product is unlikely to form by a strictly electrophilic process under these reaction conditions. Oxygen-containing substrates (esters) were also found to fluorinate productively. For example, *n*-hexyl acetate fluorinates predominately on the 3- and 5- positions of the hexyl chain (**45**) (81 % total

[92] Yadav, J. S.; Subba, B. V.; Reddy, D. Narasimha, C.; Chandrakanth, D. *Tetrahedron Lett.* **2009,** *50,* 1136 – 1138.

fluorination), whereas dihydrocoumarin reacts at its benzylic position (**46**). In contrast, δ,γ-lactone fluorinates exclusively on its side chain (**47**).

4.3) MECHANISTIC INSIGHT

Although a detailed mechanistic study is forthcoming, a few observations point to the putative participation of radicals[87] (either free or metal-based) or single-electron transfer (SET) during fluorination : 1) yields in the strict absence of O_2 are much higher than in its presence;[93] 2) interference from the MeCN solvent is minimal (at least during the initial fluorination), and consistent with its sluggish reaction with free radicals.[94] 3) finally, there is precedent for Selectfluor engaging in SET chemistry.[37,95] In contrast, bare fluoro-radicals are unlikely to be major participants in the optimized reaction as they would be expected to abstract H atoms with virtually equal facility from both tertiary and secondary alkyl sites in adamantane.[96] One final piece of evidence in support of the involvement of radicals may be discerned through the use of a radical trapping agent such as 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO). When the reaction is performed under optimized reaction conditions using a stoichiometric amount of

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[93] (a) Okamura, K.; Takahashi, Y.; Miyashi, T. *J. Phys. Chem*. **1995,** *99*, 16925 – 16931. (b) Wilkinson, F. *Pure Appl. Chem*. **1997,** *69*, 851 – 856. In contrast, this observation may also be explained by suppression of the formation of catalytically deactivated Cu-O_2 complexes; see: (c) Kitajima, N.; Moro-Oka, Y. *Chem. Rev*. **1994,** *94*, 737 – 757. (d) Tyeklar, Z.; Jacobson, R.; Wei, N.; Murthy, N. N.; Zubieta, J.; Karlin, K. D. *J. Am. Chem. Soc*. **1993,** *115*, 2677 – 2689.
[94] Engel, P. S.; Lee, W. K.; Marschke, G. E.; Shine, H. J. *J. Org. Chem*. **1987,** *52*, 2813 – 2817.
[95] (a) Zhang, X.; Wang, H.; Guo, Y. *Rapid Commun. Mass Spectrom.* **2006,** *20*, 1877 – 1882. (b) Serguchev, Y. A.; Ponomarenko, M. V.; Lourie, L. F.; Fokin, A. A. *J. Phys. Org. Chem*. **2011,** *24*, 407 – 413.
[96] Poutsma, M. L. *in Free Radicals*, Vol. II (Ed.: J. K. Kochi), Wiley, New York, **1973.**

adamantane and TEMPO, only trace amounts of **31**, **32**, and **33** are evident.

4.4) CONCLUDING REMARKS

A metal catalyzed system for the direct fluorination of alkanes has been reported. Further investigations will prove essential to the elucidation of a reaction mechanism and additional study will address the utility of the reaction and its application to complex substrates and natural products.

CHAPTER 5

IRON (II)-CATALYZED BENZYLIC FLUORINATION

5.1) INTRODUCTION TO BENZYLIC FLUORINATION

Practical, direct conversions of benzylic sp^3 C-H bonds into C-F bonds offer a potentially valuable addition to the category of C-H functionalization reactions.[97] Despite developments in site-specific oxygenation,[98] amination,[99] and other halogenation methods,[100] innate benzylic fluorination remains an underdeveloped synthetic transformation,[101] one that relies heavily on the use of electrochemical methods [102] or harsh, unselective reagents.[89,90] Considering the growing importance of fluorinated compounds in drug discovery, a mild benzylic fluorination method would prove itself a useful instrument for the medicinal

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[97] (a) Bruckl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res*. **2012,** *45*, 826–839. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002,** *417*, 507–514. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011,** *40*, 4740–4761.

[98] (a) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011,** *50*, 3362–3374. (b) Guoyong, S.; Fen, W.; Xingwei, L. *Chem. Soc. Rev*. **2012,** *41*, 3651–3678. (c) Chen, M. S.; White, M. C. *Science* **2007,** *318*, 783–787. (d) Fung, Y. S.; Yan, S. C.; Wong, M. K. *Org. Biomol. Chem*. **2012,** *10*, 3122–3130

[99] Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed*. **2013,** *52*, 1739–1742. (b) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc*. **2008,** *130*, 16184–16186. (c) King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc*. **2011,** *133*, 4917–4923. (d) Takeda, Y.; Hayakawa, J.; Yano, K.; Minakata, S. *Chem. Lett*. **2012,** *41*, 1672–1674.

[100] (a) Liu, W.; Groves, J. T. *J. Am. Chem. Soc*. **2012,** *132*, 12847– 12849. (b) Goldsmith, C. R.; Coates, C. M.; Hagan, K.; Mitchell, C. A. *J. Mol. Catal. A: Chem*. **2011,** *335*, 24–30. (c) Do, H.-Q.; Daugulis, O. *Org. Lett.* **2009,** *11*, 421–423. (d) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006,** *128,* 7134–7135.

[101] Sanford et al. have recently developed a palladium-catalyzed benzylic fluorination of *N*-containing heterocycles: McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett*. **2012,** *14*, 4094–4097.

[102] (a) Toshiki, T.; Ishii, H.; Fuchigami, T. *Electrochem. Commun*. **2002,** *4*, 589–592. (b) Hou, Y.; Higashiya, S.; Fuchigami, T. *Electrochim. Acta* **2000,** 45, 3005–3010.

chemist (e.g., allowing inhibition of cytochrome P450 oxidation and increasing the lifetime of a drug in vivo, among other applications).[45]

5.2) METAL CATALYZED METHODOLOGY

Our laboratory has recently taken an interest in the development of mild, straightforward, sp^3 C-H fluorination methods.[103] Prior to this work, both we (copper(I) bisimine, Selectfluor)[103] and the Groves group (manganese porphyrin, fluoride ion, iodosobenzene[104]) have reported unique catalytic systems for the selective fluorination of aliphatic C-H bonds. In our original copper system, it was found that, although applicable to a select few benzylic substrates, fluorination proved somewhat difficult, notwithstanding the enhanced reactivity of benzylic C-H bonds. Inspired by the oxidation capabilities of certain biological catalysts, cost-effectiveness, commercial availability, and ease of preparation, iron catalysts were investigated as a replacement for copper. We gathered that changing the catalyst could perhaps lead to a more general substrate scope, one that included benzylic compounds.

Noting previous success in the literature regarding C-H bond functionalization by nonheme iron catalysts,[105] it was reasoned that iron(II) salts

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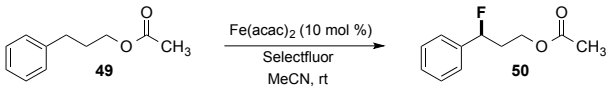
[103] Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012,** *51*, 10580–10583.
[104] Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W.; Groves, J. T. *Science* **2012,** *337*, 1322–1325.
[105] (a) Xiaoli, S.; Li, J.; Huang, X.; Sun, C. *Curr. Inorg. Chem.* **2012,** *2*, 64–85. (b) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008,** *47*, 3317–3321.

could be effective for this transformation. As such, a survey of iron salts were screened as potential catalysts using 3-phenylpropyl acetate (**49**) as a model substrate, and Selectfluor as an electrophilic source of fluorine.

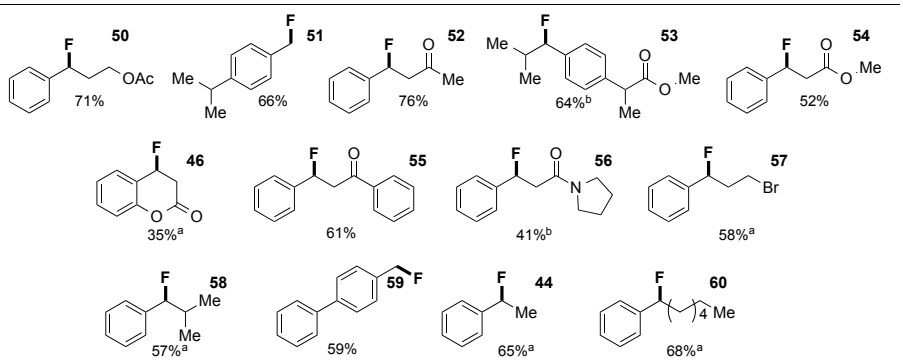
Scheme 5.1. Iron(II) catalyzed benzylic fluorination



Among the iron salts screened, only $Fe(acac)_2$ yielded the desired 3-fluoro-3-phenylpropyl acetate (**50)** (Scheme 5.1). The use of other iron salts, e.g., halides, sulfates, and nitrates, failed to yield any fluorinated products under the specified conditions. Perhaps this can be explained by the fact that hard, polydentate *O*-donor ligands, such as anionic acetylacetonate, allow easy access to higher oxidation states, facilitating oxidative functionalization. This rationale has been used to explain the activation of remote C-H bonds by late-transition-metal complexes containing one or more acetylacetonate (acac) ligands.[106]

[106] (a) Ess, D. H.; Gunnoe, T. B.; Cundari, T. R.; Goddard, W. A., III; Periana, R. A. *Organometallics* **2010,** *29*, 6801–6815. (b) Bischof, S. M.; Ess, D. H.; Meier, S. K.; Oxgaard, J.; Nielsen, R. J.; Bhalla, G.; Goddard, W. A., III; Periana, R. A. *Organometallics* **2010,** *29*, 742–756. (c) Salavati-Niasari,M.; Elzami,M. R.;Mansournia,M. R.; Hydarzadeh, S. *J. Mol. Catal. A: Chem*. **2004,** *221*, 169–175.

Table 5.1. Survey of benzylic fluorinated products

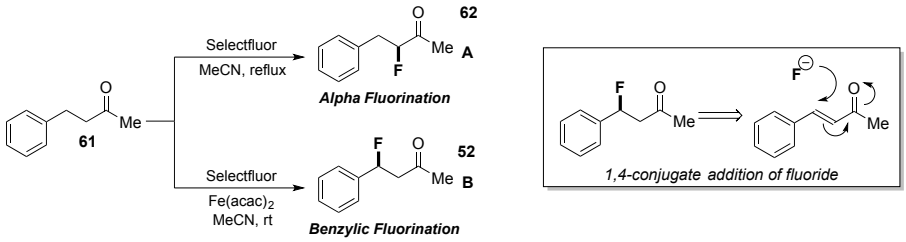


(a) Yields determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard. (b) Isolated as the major benzylic product with minor fluorinated isomers. All reactions were performed at room temperature over 24 h unless otherwise stated.

Having identified a catalyst for benzylic fluorination, the scope of the reaction was examined for a series of benzylic substrates (Table 5.1). Gratifyingly, several substrates underwent sufficient benzylic fluorination in good yields and in excellent selectivity. Some general observations were as follows: (1) Electron-poor or more neutral alkyl benzenes proved most promising, whereas electron-rich aromatic systems lead to varying quantities of polyfluorinated products, often ring fluorination adducts.[107] (2) A particularly interesting case, cymene, afforded fluorinated **51** exclusively, in direct contrast to our previously reported copper system in which fluorination of the tertiary carbon is preferred. The formation of **51** may be suggestive of a change in mechanism whereby steric constraints influence selectivity more so than trends in radical stability. (3) Carbonyl-containing compounds demonstrated a notable shift in selectivity to benzylic fluorination over an expected background reaction (Scheme 5.2).

[107] We have found that Selectfluor may fluorinate activated aromatic compounds in the absence of a catalyst.

Scheme 5.2. Iron(II) catalyzed change in selectivity for the fluorination of 3-phenyl ketones



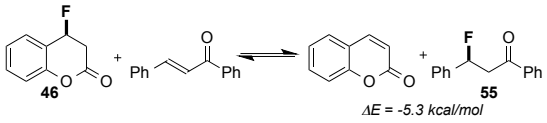
Traditionally, Selectfluor is known to react with carbonyl- containing compounds to yield α-fluorinated products.[108] For example, benzylacetone (**61**) reacts readily with Selectfluor at elevated temperatures in acetonitrile to yield α-fluorinated ketone **62** (Scheme 5.2, path A). Interestingly enough, under our catalytic conditions, benzylacetone reacts at room temperature to give benzylic fluorinated compound **52** (Scheme 5.2, path B) *exclusively*. What is more, **52** would be the retrosynthetic product of a 1,4-conjugate addition of a fluoride anion to the analogous α,β-unsaturated ketone, an attractive transformation in modern synthetic chemistry. In a similar instance, ibuprofen methyl ester affords predominantly benzylic fluorinated **53** under our conditions, potentially a pharmaceutically interesting transformation, rather than the α-fluorinated ketone. Clearly, iron is crucial in reaction selectivity favoring the benzylic position over chemistry at the more acidic α-carbon. More so, the system is highly tolerable as aryl ketones, esters, aliphatic ketones, amides, and other halogenated substrates fluorinate with near equal propensity.

[108] (a) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1996,** *37*, 3591– 3594. (b) Stavber, G.; Zupan, M.; Stavber, S. Synlett **2009,** *4*, 589–594.

5.3) COMPUTATIONAL INSIGHT

It is important to note that the majority of our substrates do not undergo dehydrohalogenation upon workup, a commonly encountered problem in benzylic halogenation. Surprisingly, β-fluoro ketones proved particularly stable, contrary to our previous finding that 2-fluorodihydrocoumarin **45** readily dehydrofluorinates. In this instance, analysis of an isodesmic reaction between a compound which readily dehydrofluorinates, fluorodihydrocoumarin **46**, and one which does not, fluorodihydrochalcone **55**, offers some insight (Scheme 5.3). At the B3LYP/6-311^{++}G** level of theory, ΔE of the isodesmic reaction is -5.3 kcal/mol,[109] suggesting a more exothermic process, whereby fluorine is lost in favor of desaturation and resultant gain in the aromatic character of coumarin.

Scheme 5.3. Isodesmic reaction for dehydrofluorination of fluorodihydrocoumarin



5.4) CONCLUDING REMARKS

Future studies will seek to elucidate the mechanism of this reaction through kinetic, isotopic, and spectroscopic analysis. In all, this method represents a

[109] Geometry optimizations were performed using the Spartan '10 program, Wavefunction, Inc.

pratical strategy for direct benzylic fluorination. Additionally, efforts will be made in the way of rendering the reaction enantioselective, an important goal in direct fluorination methods, and determining the role of carbonyls as possible directing groups for fluorination.

CHAPTER 6

METAL-CATALYZED BENZYLIC FLUORINATION AS A SYNTHETIC EQUIVALENT TO 1,4-CONJUGATE ADDITION OF FLUORIDE

6.1) INTRODUCTION TO β-FLUORINATION

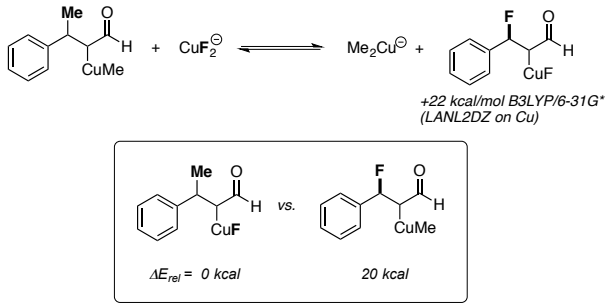
Over the past decade the demand for fluorine-enriched compounds has risen dramatically. Consequently, a host of fluorination strategies has evolved to aid the modern chemist in their syntheses.[83] Despite a large repertoire of practical fluorination methods, the 1,4-addition of fluoride to α,β-unsaturated carbonyl-containing compounds represents a long-standing problem. Of medicinal interest, hydrogen atoms β to a carbonyl are often labile and susceptible to enzymatic decomposition (e.g., in fatty acid catabolism).[110] Accordingly, the replacement of a single hydrogen atom by fluorine has been shown to increase the chemical integrity of the parent molecule, improving its lifetime *in vivo*.[45,46] It therefore stands to reason that a practical β-fluorination may prove to be a valuable transformation.

[110] (a) Campbell, N. H.; Smith, D. L.; Reszka, A. P.; Neidle, S.; O'Hagan, D. Org. *Biomol. Chem.* **2011,** *9*, 1328–1331. (b) Tang, W.; Borel, A. G.; Fujimiya, T.; Abbott, F. S. *Chem. Res. Toxicol.* **1995,** *8*, 671–682.

6.2) METAL CATALYZED METHODOLOGY

Previous efforts exploring the use of cuprates (copper fluorides) have yet to afford a notable success, resulting in trace yields or limited selectivity.[111] Perhaps this is no surprise; computationally, employing hybrid-DFT theory, the addition of dimethylcuprate is predicted to be much more thermodynamically favorable than the addition of CuF_2^- (Scheme 6.1).

Scheme 6.1. Computational analysis of cuprates in fluoride conjugate addition



Alternatively, an indirect, and more subtle approach can be envisioned whereby fluorination of a β C-H bond is performed in the absence of the alkene, eliminating the need for conjugate addition or hydrofluorination.[112,113] Recently,

[111] For a review of cuprates in conjugate additions, see: (a) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012,** *44*, 3109–3128. (b) Mori, S.; Nakamura, E. *Modern Organocopper Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, **2002**; pp 315–346. (c) Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988,** *60*, 57–64.

[112] Our group has recently published a direct method for alkane. Groves et al. have likewise published on a catalytic method for alkane fluorination using a manganese porphyrin, iodosylbenzene as an oxidant, and AgF as a source of fluoride anion: (ref 103 and 104).

[113] (a) Sanford et al. have recently developed a ligand directed palladium-catalyzed benzylic fluorination of *N*-containing heterocycles (ref 101). (b) Groves et al. and Inoue et al. have also

our lab published an iron(II)-catalyzed system for the chemoselective benzylic fluorination of several alkylbenzenes using Selectfluor as a fluorinating agent.[114] Our paper was among the first to provide a more general solution to what is proving to be a very timely problem.[115] While examining the scope of this reaction, it was found that 3-phenylketones (e.g. compound **61**) reacted to afford benzylic fluorinated products instead of the expected, and often competitive α-fluorinated products.[108] Taking advantage of this anomalous reactivity, the iron-catalyzed benzylic fluorination of substrates containing aromatic rings and electron-withdrawing groups beta (β) to one another has been explored in more detail to prepare previously inacessible β-fluorinated products (Scheme 6.2). All together, this process can be thought of as a functional solution to the long-standing problem of mild conjugate addition of fluoride, affording products in good to moderate yields and in excellent selectivity. Furthermore, this system could also be used as a surrogate to harsh, traditional methods involving nucleophilic-conjugate addition with hydrohalic acids,[116,117] providing a direct, convenient route for site-specific β-fluorination.

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reported direct methods for benzylic fluorination: Liu, W.; Groves, J. T. *Angew. Chem., Int. Ed.* **2013,** *52*, 6024–6027. (c) Amaoka, Y.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013,** *15*, 2160–2163.

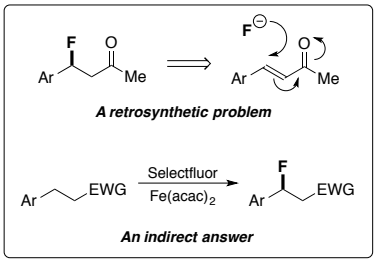
[114] Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T. *Org. Lett.* **2013,** *15*, 1722–1724.

[115] The popularity of iron catalysts for the direct functionalization of nonactivated sp^3 C-H bonds has grown considerably in recent years. For representative examples, see: (a) Sekine, M.; Ilies, L.; Nakamura, E. *Org. Lett.* **2013,** *15*, 714–717. (b) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012,** *134*, 2036–2039. (c) Song, C.-X.; Cai, G.-X.; Farrell, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B.; Shi, Z.-J. *Chem. Commun.* **2009,** 6002–6004.

[116] German, L. S.; Knunyantz, I. L. *Angew. Chem., Int. Ed. Engl.* **1969,** *8*, 349–356.

[117] Jacobs, W. A.; Heidelberger, M. *J. Am. Chem. Soc.* **1917,** *39*, 1465–1466.

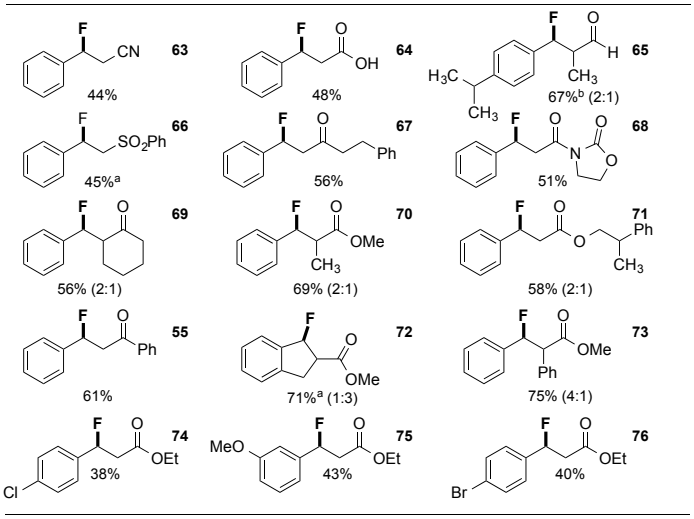
Scheme 6.2. Iron(II) catalyzed benzylic fluorination as a retrosynthetic equivalent to the 1,4-conjugate addition of fluoride



In examining several well-known, saturated variants of "Michael acceptors" under catalytic conditions it was found that a host β-fluorinated products could be obtained in good yields and in outstanding selectivity (Table 6.1). Some noteworthy observations include (1) α-substituted carbonyls demonstrated a preference for *syn* addition of fluorine; (2) nitriles, aldehydes, and free acids were tolerated under our reaction conditions despite a perceived high propensity for deleterious side reactions with Selectfluor and various metal catalysts;[118] (3) for substrates possessing multiple benzylic positions **65**, **67**, **71**, and **73**, fluorination of the least substituted carbon is preferred; (4) difluorination and (5) α-fluorination are negligible. In addition, 1,3-aryl sulfones, ketones, and oxazolidinones were successfully β-fluorinated, the latter being a potentially useful auxiliary for developing an asymmetric variant of this reaction.

[118] (a) Peng, W.; Shreeve, J. M. *Tetrahedron Lett.* **2005,** *46*, 4905– 4909.

Table 6.1. Survey of 1,4-conjugate addition products

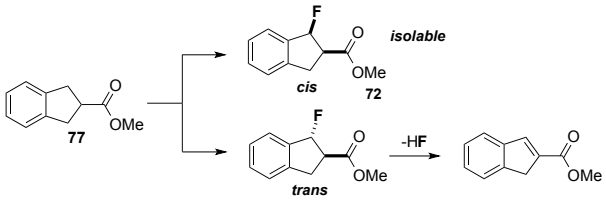


(a) Yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard. (b) Isolated as the major benzylic product with minor fluorinated isomers. All reactions were run at room temperature for 24 h unless otherwise stated. Diastereoselectivity is reported as (*syn* : *anti*).

β-fluorinations of several pharmaceutically efficacious scaffolds including cyclamen (**65**), the 3-phenylpropylester (**71**), chalcone (**55**), and the indane (**72**) were also achieved. Among these structures, indane (**77**) proved a particularly interesting case. By crude ^{19}F NMR, both *trans* and *cis* diastereomers are produced in a 3:1 ratio. However, upon purification by silica gel chromatography, only the *cis* diastereomer can be isolated (31%). In the case of the *anti* diastereomer, a rapid dehydrofluorination occurs to furnish the unsaturated indene as characterized by ^{1}H NMR. The instability of the *trans* isomer relative to *cis* is rationalized given the ease of syn-elimination based on precedent in related

systems (see Scheme 6.3).[119] Degradation of the *cis*-diastereomer may be likewise expected, albeit at a much slower rate.

Scheme 6.3. Dehydrofluorination of the *trans*-diastereomer



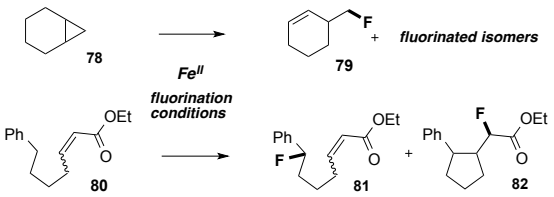
6.3) MECHANISTIC INSIGHT

Although applicable to a wide survey of functional groups, yields for this reaction trended for highly electron-withdrawing "Michael acceptors" in the general order COOMe > COOH > SO_2Ph > CN > NO_2 (trace amounts). This correlates nicely with relative σ-substituent values, advocating an increased reactivity of more oxidizable, electron-rich benzylic hydrogens toward fluorination, an unsurprising finding assuming the possible involvement of free radicals during the reaction.[120,121] To test for the involvement of radicals in this reaction the strained cycloalkane norcarane **78** was used in a radical clock experiment.

[119] (a) Hudlicky, M. Collect. Czech. *Chem. Commun*. **1991,** *56,* 1680−1689. (b) Bartsch, R. A.; Zavada, J.́ *Chem. Rev*. **1980,** *80*, 453– 494. (c) Sicher, J. *Angew. Chem., Int. Ed*. **1972,** *11*, 200–214.
[120] For a complete table of σ values, see: (a) Datta, D. J. *J. Phys. Org. Chem*. **1991,** *4*, 96–100. (b) McDaniel, D. H.; Brown, H. C. *J. Org. Chem*. **1958,** *23*, 420–427.
[121] Iron acetylacetonates are known to participate in radical based transformations. See: (a) Barker, T. J.; Boger, D. L. *J. Am. Chem. Soc*. **2012,** *134*, 13588–13591. (b) Xue, Z.; Poli, R. *J. Polym. Sci., Part A: Polym. Chem*. **2013,** *51*, 3494–3504. (c) Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Beilstein J. Org. Chem*. **2013,** *9*, 1718–1723.

Although not a benzylic substrate per se, the cyclopropane ring is similarly activating. Homolytic cleavage of a C3 C-H bond should lead to product **79** following a rapid opening of the cyclopropyl ring and trapping with fluorine (Scheme 6.4).[87] In a similar fashion, α,β-unsaturated aryl ester **80** should be a propitious substrate to probe the generation of benzylic radicals. It is expected that formation of the corresponding benzyl radical could lead to the standard fluorinated product **81** and/or to the more diagnostic product **82** through a cyclization reaction. In both cases, these putative radical-derived products were observed by ^{19}F NMR analysis and identified by comparison to known literature values.[122,123]

Scheme 6.4. Preliminary evidence for the involvement of radical during fluorination



In the case of **78**, it should be noted that the primary fluoride **79** is still the predominant product. Whereas the formation of **79** is incompatible with an anionic mechanism, the formation of cyclized product **82** is incompatible with a cationic mechanism.

[122] For spectral data see: Morikawa, T.; Uchida, J.; Hasegawa, Y.; Takeo, T. *Chem. Pharm. Bull.* **1991,** *39*, 2462–2464.
[123] For spectral data see: ref 104.

6.4) CONCLUDING REMARKS

In conclusion, a convenient, mild route for the direct preparation of β-fluorinated, 3-phenyl propanoids has been presented. This protocol is operationally reliable, highly chemoselective, and has been shown to tolerate a diverse array of functional groups. What is more, this reaction can act as a surrogate in the 1,4-conjugate addition of fluoride providing an alternative to corrosive hydrofluoric acid protocols.

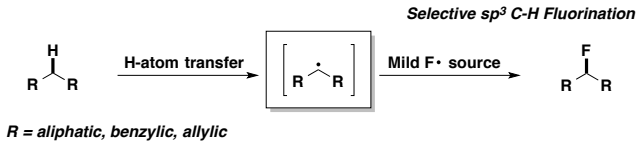
CHAPTER 7

Direct, Catalytic Monofluorination of sp^3 C-H Bonds: A Radical-Based Mechanism with Ionic Selectivity

7.1) MECHANISM FOR THE COPPER(I) CATALYZED FLUORINATION OF ALKANES

Recently, our group unveiled a system in which an unusual interplay between copper(I) and Selectfluor effects mild, catalytic sp^3 C-H fluorination. Herein, a detailed reaction mechanism based on exhaustive EPR, ^{19}F NMR, UV-Vis, electrochemical, kinetic, synthetic, and computational studies is presented that, to our surprise, was revealed to be a radical chain mechanism in which copper acts as an initiator (Scheme 7.1). Furthermore, we offer an explanation for the notable but curious preference for monofluorination by ascribing an ionic character to the transition state.

Scheme 7.1. Radical chain mechanism



Selective functionalization of sp^3 C-H bonds represents an area of invaluable and efficient chemistry. The direct formations of alcohols, alkenes, alkyl halides, and other functional groups from inactivated C-H bonds are impressive, seemingly effortless reactions accomplished by enzymes that are often challenging to effect in a laboratory setting. However, selective *fluorination* has proven an arduous undertaking for both Nature and the synthetic chemist alike. Biologically, very few fluorinase enzymes are known, and none of them operates on the basis of direct C-H functionalization.[124] Synthetically, a conceivable radical fluorination method using hazardous and difficult-to-use F_2, similar to the well-established bromination and chlorination reactions, is actually highly exothermic, which causes great selectivity and safety concerns.[125] For organofluorine chemists, this issue and other existing challenges call for a more innovative approach to C-H fluorination.

Arguably one of the most significant developments in the field of organofluorine chemistry was the advent of the *N*-F reagents (containing a nitrogen-fluorine bond) intended as mild sources of electrophilic fluorine in the late 1980s.[126] Considering that these reagents were solid, stable, and effective compounds, they quickly superseded the use of the high-energy electrophilic

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[124] (a) Eustáquio, A. S.; O'Hagan, D.; Moore, B. S. *J. Nat. Prod.* **2010,** *73*, 378-382. (b) O'Hagan, D.; Schaffrath, C.; Cobb, S. L.; Hamilton, J. T. G.; Murphy, C. D. *Nature* **2002,** *416*, 276.

[125] The chain propagation steps in the radical fluorination of an alkane using F_2 (H-atom abstraction and subsequent fluorination) have an overall change in enthalpy of approximately -103 kcal/mol.

[126] For examples: (a) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988,** *29*, 6087-6090. (b) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986,** *27*, 4465-4468. (c) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991,** *32*, 1631-1634. (d) Banks, R. E. *J. Fluorine Chem.* **1998,** *87*, 1-17, and references cited therein.

fluorinating reagents such as fluorine gas, xenon difluoride, perchloryl fluoride, and hypofluorites, making fluorination reactions significantly more accessible to the synthetic chemist.[127] Among the top ranks of the *N*-F reagents are *N*-fluorobenzene sulfonimide (NFSI), *N*-fluoropyridinium salts (NFPy), and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) *vide infra* (Figure 7.1). These unique and versatile compounds have proven their worth as reagents for fluorofunctionalization as mediators and catalysts, but are also ideal candidates for mechanistic studies.[128]

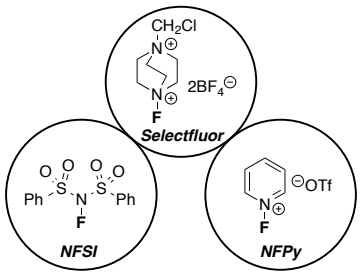


Figure 7.1. Common "N-F" reagents.

Recent findings suggest that some of these so-called "electrophilic" *N*-F reagents can also act as F-atom transfer reagents. Sammis et al. have reported the ability of NFSI to react with alkyl radicals,[129] Baran et al. have suggested the

[127] Kirsch, P. Synthesis of Complex Organofluorine Compounds. In *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications;* Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2004**; pp 203-278, and references cited therein.
[128] For some examples of studies and applications of N-F reagents, particularly Selectfluor, see: (a) Stavber, S.; Zupan, M. *Acta Chim. Slov.* **2005,** *52*, 13-26. (b) Stavber, S. *Molecules*, **2011,** *16*, 6432-6464. (c) Vincent, S. P.; Burkart, M. D.; Tsai, C-Y.; Zhang, Z.; Wong, C-H. *J. Org. Chem.* **1999,** *64*, 5264-5279. (d) Oliver, E. W.; Evans, D. H. *J. Electroanal. Chem.* **1999,** *474*, 1-8.
[129] Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012,** *134*, 4026-4029.

ability of Selectfluor to participate in single-electron transfer (SET) chemistry and the homolytic cleavage of C-H bonds,[130] and within the last year both our laboratory and the Groves laboratory have independently published methods on metal-catalyzed sp^3 C-H monofluorination. Where the Groves system utilizes silver(I) fluoride (a nucleophilic fluorine source) and iodosobenzene to generate a manganese(IV) fluoride porphyrin catalyst *in situ* instead of an aforementioned *N*-F reagent,[104] our system, as will be shown, relies fundamentally on radical-based chemistry between Selectfluor and a copper(I) promoter to effect both H-atom abstraction and subsequent installation of fluorine.[103]

Groves's and our work were among the first direct, catalytic methodologies for the monofluorination of aliphatic substrates. These discoveries prompted further investigations in our laboratory, *viz.* 1) simplification of the conditions for our originally fairly complex system, 2) exploration of the chemistry of other redox-active transition metals with Selectfluor,[114] and especially 3) in-depth mechanistic studies of the system(s) we devised.

The following is structured to present a logical narrative whereby the mechanistic studies were conducted. With this regard, the information is organized respectively as to 1) establish the simplified protocol used for mechanistic analysis, 2) discuss the experiments used to determine the role of copper as an initiator, 3) examine the H-atom abstraction/fluorination steps of the mechanism (illuminating the involvement of radical intermediates), 4) illustrate

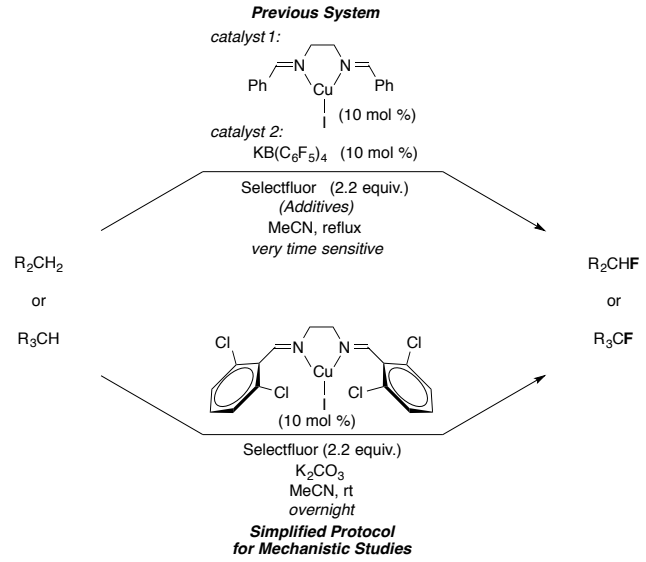
[130] Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012,** *134*, 2547-2550.

our conclusions drawn from kinetic analyses, 5) propose a reasonable mechanism in accord with all experimental observations, and 6) offer an explanation for the observed selectivity of our reaction as a manifestation of the "polar effect" by ascribing an ionic character to the H-atom abstraction transition state and, finally, subjecting the system to computational analysis to confirm experimental results.

7.2) SIMPLIFIED PROTOCOL

Our original discovery combined Selectfluor and transition metal catalysts (especially copper(I) based complexes) in effecting direct aliphatic, benzylic, and, in special cases, allylic monofluorination.[103,114] However, the copper system that focused on aliphatic fluorination, albeit intriguing, is admittedly less practical for large-scale applications as it involves the use of several additives. Thus, our immediate goal was to establish a simplified protocol that is more accessible, cost-effective, scalable, less time-sensitive, and easier to subject to mechanistic studies. A logical approach was to strip the system back down to the minimum number of necessary components (i.e. Selectfluor, a copper salt, acetonitrile) and address possible problems more directly (Scheme 7.2).

Scheme 7.2. Simplified protocol for alkane fluorination



Previously, we observed that our newly fluorinated substrates were prone to ionization *in situ* over time, which led to a decrease in product yields if the reactions were not quenched at the appropriate time intervals. Perhaps this is attributed to a gradual accumulation of hydrogen fluoride (HF) as a byproduct of the reaction, which was observed by ^{19}F NMR under our published conditions. To prevent the buildup of HF, we screened a variety of bases and noted that whereas amines often impede the reaction altogether, 0.1 equiv. of potassium carbonate is often enough to effect the reaction and eliminate any traces of HF by ^{19}F NMR for 16-24 h. This small modification allows us to let a variety of substrates stir at room temperature for longer, generalized periods of time without having vigilantly to monitor and optimize each one individually. To our satisfaction, we also obtained comparable conversions to monofluorinated products in the presence of potassium carbonate. However, at this time we did

not conclude anything about the true role of the potassium carbonate in the system.

Hoping to circumvent the dependency on potassium tetrakis(pentafluorophenyl)borate, *N*-hydroxyphthalimide, and potassium iodide for higher yields, we decided to focus on modifying the ligand. In the original system, we had the most success with *N,N'*-bis(benzylidene)ethane-1,2-diamine. Making minor modifications to the ligand scaffold, we quickly found a substantial increase in percent conversions at room temperature by using *N,N'*-bis(2,6-dichloro-benzylidene)-ethane-1,2-diamine instead.[131] At this juncture in our laboratory, we have established that a standard reaction using 2.2 equiv. Selectfluor, 0.1 equiv. cuprous iodide, 0.1 equiv. of the aforementioned ligand, and 0.1-1.0 equiv. potassium carbonate in MeCN under N_2 at room temperature overnight was a suitable, generalized protocol for aliphatic and benzylic monofluorination (Scheme 7.2). Under these conditions, the reaction has also proven amenable to gram-scale synthesis of monofluorinated products (e.g. 1-fluorocyclododecane was obtained in 50% yield after 8 h). Using this simplified protocol, we sought to address the most fundamental concerns surrounding the reaction mechanism, i.e. the role of copper, how the fluorine atom is installed, how the reaction kinetics behave, and the preference for monofluorination.

[131] Both *N,N'*-bis(benzylidene)ethane-1,2-diamine and *N,N'*-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine were synthesized according to literature procedure. See: Liu, H.; Zhang, H-L.; Wang, S-J.; Mi, A-Q.; Jiang, Y-Z.; Gong, L-Z. *Tetrahedron: Asymmetry* **2005,** *16*, 2901-2907.

7.3) LOSS OF FLUORIDE FROM COPPER(I)-SELECTFLUOR INTERACTION

Intuitively, copper can either be a species actively involved in the catalytic cycle or an initiator to the reaction. With these potential roles in mind, a large array of experiments was designed to probe the behavior of copper over the course of the reaction.

Considering that the minimum necessary components to cause sp^3 C-H fluorination are simply Selectfluor and copper(I), we first studied their interaction by NMR. A ^{19}F NMR spectrum of Selectfluor in CD_3CN displays an *N*-F signal at +47.1 ppm and a BF_4 signal at -152.1 ppm, relative to 3-chlorobenzotrifluoride.[132] A spectrum of a 1:1 mixture of Selectfluor and cuprous iodide in CD_3CN, taken after 45 min of stirring, displays a BF_4 signal at -152.4 ppm and the standard peak. No *N*-F fluorine signal is observed at +47.1 ppm, nor are any additional signals from +400 ppm to -300 ppm present.

Preliminary EPR experiments reveal the formation of a copper(II) species, but no Cu-F coupling is observed at room temperature, as well. So where did the fluorine atom go? The most logical scenario is the formation of a copper fluoride species that is undetectable by ^{19}F NMR due to extreme signal broadening induced by the paramagnetic copper(II) center (unlikely), formation of a copper(II) bifluoride exhibiting fluxional behavior in solution,[133] or the fact that after rapid

[132] Naumann, D.; Kischkewitz, J. *J. Fluorine Chem.* **1990,** *47*, 283-299.

[133] Roe, C. D.; Marshall, W. J.; Davidson, F.; Soper, P. D.; Grushin, V. V. *Organometallics* **2000,** *19*, 4575-4582.

solvolysis, it exists as a solvent separated ion pair.[134] Attempts were made to "freeze out" a copper(II) bifluoride signal at -10 ^{o}C and -40 ^{o}C, but no evidence for this type of species or any other signal was seen. Notably, a simple ^{19}F NMR of cupric fluoride in MeCN supports the notion of solvent separation – no fluorine signal is observed.

To rule out the possibility of a copper fluoride formed *in situ* being the key player for H-atom abstraction and subsequent installation of fluorine, several control experiments were run using preformed copper fluorides (cupric fluoride and $(PPh_3)_3CuF_2MeOH$)[135] in the absence of Selectfluor.[136] Although these experiments provide no evidence for/against a copper fluoride as the source of fluorine during the fluorination step of the mechanism,[137] they do help confirm that an interaction between copper and Selectfluor is necessary to generate the species responsible for effecting H-atom abstraction.[138]

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[134] Baxter, A. C.; Cameron, J. H.; McAuley, A.; McLaren, F. M.; Winfield, J. M. *J. Fluorine Chem.* **1977,** *10*, 289-298.

[135] For syntheses of stabilized copper(I) fluoride complexes, see: (a) Jardine, F. H.; Rule, L.; Vohra, A. G. *J. Chem. Soc. (A)* **1970,** 238-240. (b) Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981,** *52*, 153-159.

[136] Another control experiment was also designed to probe the involvement of a copper(III) fluoride by applying a (2-pyridyl)methylamine ligand to the system, which has been shown to promote two-electron chemistry in copper(I) complexes, but no positive ligand effects were observed. See: Osaka, T.; Karlin, K. D.; Itoh, S. *Inorg. Chem.* **2005,** *44*, 410-415.

[137] Another control experiment conducted was a thermolysis of *tert*-butyl 2-phenylpropaneperoxoate in the presence of cupric fluoride under Sammis's conditions that could conceivably illuminate how an alkyl radical reacts with a copper(II) fluoride. No 1-fluoroethylbenzene was observed; however, these conditions do not directly mimic the reaction conditions.

[138] Note that the reaction does not produce fluorinated products under the reaction conditions with Selectfluor in the absence of copper either; this control reaction was conducted.

7.4) UV-VIS AND EPR ANALYSES INDICATE COPPER(II) SPECIES

This copper(I)-Selectfluor interplay may best be elucidated by direct observation of copper. Formation of a copper(II) species was recognized early on in the investigation by UV-Vis and EPR analyses, and was subsequently studied intently.

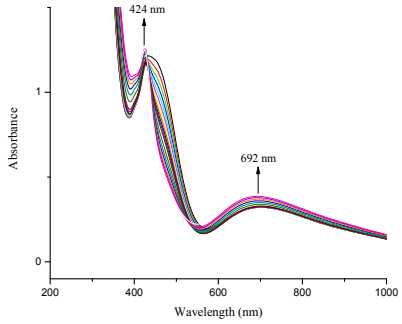


Figure 7.2. UV-Vis spectra of CuI, ligand, and Selectfluor.

UV-Vis spectroscopy was used to monitor changes in the copper species early in the reaction (ca. t = 5 min to t = 15 min displayed in Figure 7.2). Figure 7.2 displays visible bands at 426, 456, and 692 nm upon the addition of cuprous iodide and our bis(imine) ligand to Selectfluor in MeCN under N_2. The broad band at 692 nm, a new copper(II) absorbance, grows in concomitantly with the sharp absorbance at 426 nm, which disappears in the absence of ligand and is conceivably a charge-transfer band from a copper-ligand interaction. The decreasing absorbance at 456 nm was determined to result from an interaction

between iodide and Selectfluor - this absorbance was duplicated when taking a UV-Vis spectrum upon mixing Selectfluor with tetrabutylammonium iodide (note that the interaction between iodide and Selectfluor alone will not effect the fluorination reaction; copper is necessary). Interestingly, when the reaction was run in a cuvette under standard conditions (in the presence of substrate), the spectrum obtained was virtually identical. Furthermore, a UV-Vis spectrum taken after several hours still shows a strong copper(II) absorbance.

The formation of a paramagnetic copper(II) species presents an opportunity for analysis via EPR spectroscopy. For liquid phase EPR experiments, a flat-cell was used in place of a cylindrical sample configuration in order to minimize the absorption of microwaves by the solvent.[139] The copper(II) spectra of reaction conditions with and without a substrate present consist of four hyperfine lines (from copper; $I = 3/2$) of unequal intensities that grow in and *persist* over time. Subsequent observation of a reaction in the absence of a substrate over time revealed gradual shifts in intensities and resonances (Figure 7.3). This could indicate a change in geometry or ligand environment of the original copper(II) species formed. For better clarification, we turned to solid-state EPR.

The added complexity of solid-state EPR spectra due to anisotropic effects can illuminate details about the geometry of a complex, symmetry, and the nature

[139] MeCN is a high dielectric solvent and makes for a "lossy" sample, which can be overcome with a flat-cell. See: (a) Hyde, J. S. *Rev. Sci. Instrum.* **1972,** *43*, 629-631. (b) Mett, R. R.; Hyde, J. S. *J. Magn. Reson.* **2003,** *165*, 137-152. (c) Sidabras, J. W.; Mett, R. R.; Hyde, J. S. *J. Magn. Reson.* **2005,** *172*, 333-341. (d) Eaton, S. S.; Eaton, G. R. *Anal. Chem.* **1977,** *49*, 1277-1278.

of any neighboring atoms.[140] In an attempt to achieve optimal resolution, spectra were collected at 8 K using isotopically enriched ^{63}CuI and ^{15}N-labeled ligand (Figure 7.4).[141] To our knowledge, this is the best approach to determine definitively whether a direct Cu-F interaction is characteristic of the copper species at any point in the reaction.

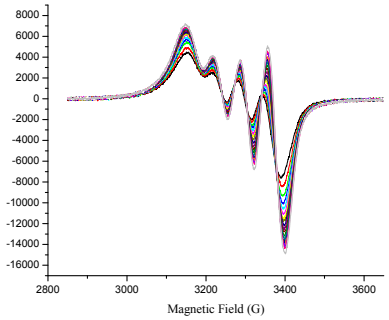


Figure 7.3. Flat-cell liquid phase spectra of copper(II) over time.

Solid-state spectra of the reaction in the absence of a substrate display an interesting feature. An equilibrium of two copper(II) species is well resolved in a spectrum taken after 3 h (Figure 7.5). The signatures indicate that both species are monomeric, solely surrounded by nitrogen-containing ligands, and tetragonal

[140] Bennati, M.; Murphy, D. M. Electron Paramagnetic Resonance Spectra in the Solid State. In *Electron Paramagnetic Resonance: A Practitioner's Toolkit*; Brustolon, M.; Giamello, E., Eds. John Wiley & Sons, Inc.: Hoboken, NJ, **2009**; pp 195-250.

[141] The natural abundance of ^{63}Cu:^{65}Cu is about 70:30 (I = $^{3}/_{2}$ in both instances) and ^{14}N:^{15}N is over 99:1, but ^{15}N (I = -½) gives rise to a simpler (doublet vs. triplet for ^{14}N), more pronounced superhyperfine pattern (A(^{15}N)/A(^{14}N) = 1.4). For some applications, see: (a) Yuan, H.; Collins, M. L. P.; Antholine, W. E. *Biophys. J.* **1999,** *76*, 2223-2229. (b) Lemos, S. S.; Collins, M. L. P.; Eaton, S. S.; Eaton, G. R.; Antholine, W. E. *Biophys. J.* **2000,** *79*, 1085-1094.

in coordination geometry ($g_{\parallel} > g_{\perp} > g_e$; see Table 7.1).[142] Although it is tempting to mistake the separation of the hyperfine resonances for each species as "splitting," perhaps due to a Cu-F interaction, none is observed – these are two separate copper complexes that both lack coupling to fluorine. Regarding the implausibility of a Cu-F interaction, Weltner et al. reported a hyperfine coupling constant of $A(^{19}F)$ = 115 G derived from EPR spectra of cupric fluoride at 4 K in argon and neon matrices, which is significantly higher than any supposed splitting observed in these complexes, but may not be the most appropriate comparison.[143] In another scenario, by exposing ceruloplasmin to 15 equiv. of fluoride, Gray et al. reported $A(^{19}F)$ = 40 G for a cupric fluoride,[144] which seems on par with the separation between our observed hyperfine resonances. Yet, the additional g_3 resonance that appears in our spectra shatters the appeal of perceiving this as Cu-F coupling and solidifies the notion of two separate copper(II) complexes.[145]

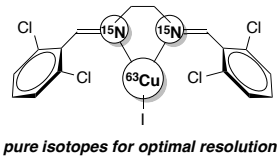


Figure 7.4. Isotopically enriched ligand for solid state EPR.

[142] Majahan, M.; Saxena, K. N.; Saxena, C. P. *J. Inorg. Nucl. Chem.* **1981,** *43,* 2148-2152.
[143] Kasai, P. H.; Whipple, E. B.; Weltner, W. *J. Chem. Phys.* **1966,** *44*, 2581-2591.
[144] Dawson, J. H.; Dooley, D. M.; Gray, H. B. *Proc. Natl. Acad. Sci. USA* **1978,** *75*, 4078-4081.
[145] Despite optimal conditions with pure isotopes, no additional information on ligand binding could be obtained via EPR spectroscopy without access to instrumentation capable of ENDOR.

In the presence of substrate (under standard reaction conditions), something even more interesting is observed – the presence of only one of the two copper(II) species (Figure 7.6). This is likely an issue of dynamic ligand activity between the putative complexes (Scheme 7.3). A higher concentration of an additional amine ligand (Selectfluor minus F^+) is formed under reaction conditions, which shifts the equilibrium preferentially toward only one of the copper(II) species.

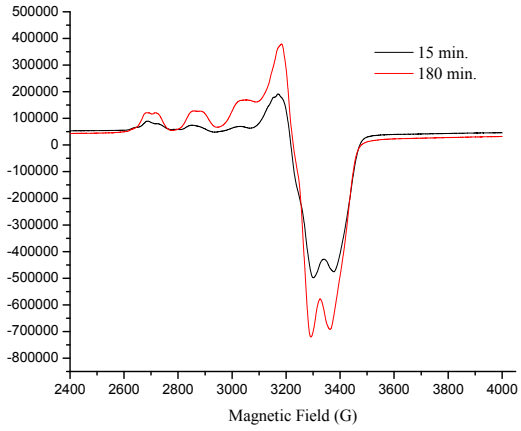


Figure 7.5. Solid-state spectra of copper(II) in the absence of a substrate at 8 K.

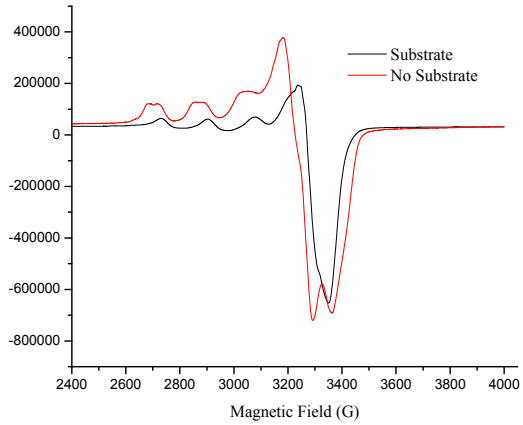


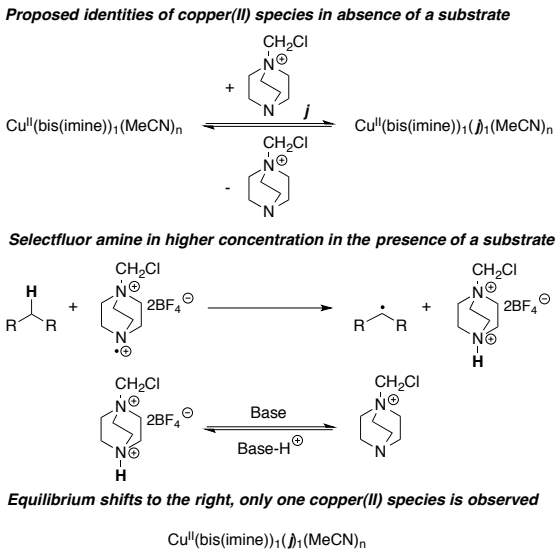
Figure 7.6. Solid-state spectra of copper(II) after 180 min. with (**C1**) and without (**C2**) substrate present at 8 K.

Table 7.1. EPR parameters for complexes in Figures 7.5 and 7.6

$g_{\|}$	$g_{\perp}$	$A_{\|}$(G)	$A_{\perp}$(G)	g_{iso}	A_{iso} (G)
2.27	2.04	170	12.5	2.12	65
2.30	2.12	177	16.5	2.18	70
2.28	2.07	167	14.0	2.14	65

In the catalytic cycle we ultimately propose, a radical dication abstracts a hydrogen atom from an alkane to form an ammonium salt, which would easily be deprotonated in the presence of potassium carbonate (Scheme 7.3). The corresponding amine would be a suitable ligand for copper(II). If an alkane substrate is not present, the formation of protonated amine is significantly slower, the concentration of the amine significantly lower, and thus, there is a mixture of amine-ligated copper(II) and non-amine-ligated copper(II). This is consistent with the EPR parameters for the complexes (Table 7.1), which indicate that both

copper species are surrounded solely by nitrogen-containing ligands. Under any circumstance, there is no observed Cu-F interaction, characteristic of a copper(II) bifluoride or otherwise. It is crucial to highlight that this by no means rules out the possibility of a solvent separated copper(II) fluoride being formed as a product of the reaction, which can be inferred reasonably from our NMR experiments.



Scheme 7.3. Possible intermediates in alkane fluorination

Lastly, hoping for more clarification, several attempts were made to grow single crystals suitable for X-ray structure determination of the unoxidized copper(I)-bis(imine) complex and the oxidized copper(II) species observed by EPR. In the former scenario, an interesting polymeric structure was obtained exhibiting 2:1 cuprous iodide:bis(imine) ligand stoichiometry. However, this polymer is likely just a thermodynamic sink for the copper(I):bis(imine) ligand interaction and does not play an active role in the chemistry; EPR signatures of

the copper(II) species observed over the course of the reaction do not resemble those of dimeric or polymeric copper species.[146] In the latter scenario, any attempt to grow crystals of the oxidized copper species (in the presence of Selectfluor) only afforded the ammonium salt H-TEDA-BF_4 - previously reported by the Baran group.[130]

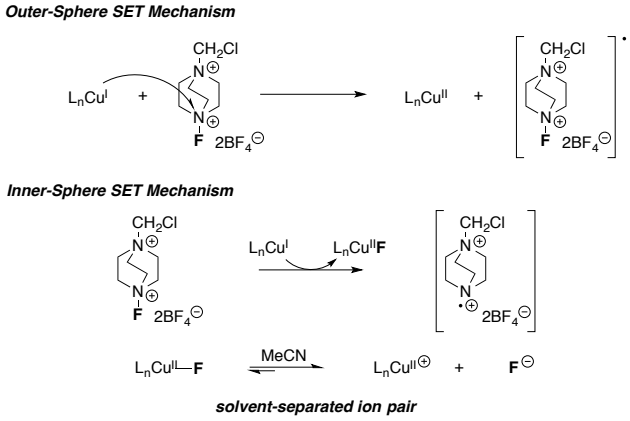
7.5) INITIATION BY SINGLE-ELECTRON TRANSFER

Evidence of a rapid growth and persistence of copper(II) over the course of the reaction was observed in the liquid phase EPR studies, whereby copper(II) is formed rapidly over the first hour of the reaction (~85% conversion from copper(I)) and asymptotically approaches 100% conversion thereafter.[147] It is very possible that the copper species plays a *laissez-faire* role beyond initiating the reaction and generating an unstable Selectfluor derivative that serves as the H-atom abstractor and propagator in the reaction mechanism. Taking into account previous observations by both our laboratory and the Baran laboratory, we explored the supposed SET chemistry between copper and Selectfluor. There are two potential scenarios to consider under the reaction conditions,

[146] For instance: Moncol, J.; Mudra, M.; Lönnecke, P.; Hewitt, M.; Valko, M.; Morris, H.; Svorec, J.; Melnik, M.; Mazur, M.; Koman, M. *Inorg. Chim. Acta.* **2007,** *360*, 3213-3225.
[147] Determined by EDTA titration.

resembling either an outer-sphere or inner-sphere electron transfer mechanism (Scheme 7.4).[148]

Scheme 7.4. Electron transfer between copper(I) and Selectfluor



In the instance of an outer-sphere mechanism, the copper species and Selectfluor would remain separate and otherwise unchanged throughout the course of an event where copper(I) transfers an electron to Selectfluor, generating copper(II) and Selectfluor radical cation. One could draw out a mechanism where the radical cation performs H-atom abstraction, forming HF and an alkyl radical, and the newly formed alkyl radical reacts with Selectfluor to generate a fluorinated product and a radical dication species that would be responsible for subsequent H-atom abstraction. However, a few experimental findings discount this possibility. First of all, if this outer-sphere mechanism holds

[148] For some of the original discussion of outer-sphere and inner-sphere electron transfer mechanisms, see: (a) Marcus, R. A. *J. Chem. Phys.* **1956,** *24*, 966-978. (b) Marcus, R. A. *J. Chem. Phys.* **1956,** *24*, 979-989. (c) Taube, H.; Myers, H.; Rich, R. L. *J. Am. Chem. Soc.* ***1953,*** *75, 4118-4119.*

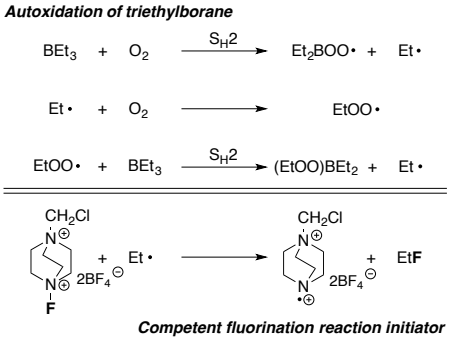
true for initiating the reaction, other known, highly competent outer-sphere single-electron transfer reagents, such as ferrocene, should be able to produce similar results upon reaction with Selectfluor.[149] Running the reaction with ferrocene instead of cuprous iodide (despite the promising color change to dark green, indicating formation of the ferrocenium ion) gave very poor results, yielding only a trace amount of the desired fluorinated product. Tris(bypyridine)ruthenium(II) also proved incompetent in effecting the reaction. Secondly, a controlled potential electrolysis experiment was attempted in the presence of an electrolyte, Selectfluor, and cyclododecane, but was unsuccessful in reducing Selectfluor while producing any detectable fluorinated products. Third of all, in the absence of base (i.e. potassium carbonate), we should be able to detect an initial burst of HF by ^{19}F NMR at room temperature, but this was not observed. Lastly, a differential pulse voltammogram (DPV) of a 1:1 mixture of copper:bis(imine) ligand reveals an oxidation potential of +0.87 V vs. SCE for the copper(II/I) transition; however, the reported reduction potential of Selectfluor, -0.296 V vs. AgRE,[150] would suggest an unfavorable flow of electrons by an outer-sphere electron transfer mechanism and further aid in the nullification of this type of process. Thus, an inner-sphere mechanism whereby a radical dication is formed may be the more likely of the two.

[149] Clegg, A. D.; Rees, N. V.; Klymenko, O. V.; Coles, B. A.; Compton, R. G. *J. Electroanal. Chem.* **2005,** *580*, 78-86.
[150] Oliver, E. W.; Evans, D. H. *J. Electroanal. Chem.* **1999,** *474*, 1-8.

Still, a more convincing argument would be to show an example where the reaction *proceeds* through another inner-sphere electron transfer event. Thus, we examined an initiator that cannot fathomably form the radical dication through an "outer-sphere" process accompanied by loss of fluoride: a primary alkyl radical. The formation of ethyl radicals *in situ* is well established upon reaction of triethylborane with oxygen.[1] Applying this chemistry to our system, an ethyl radical could reasonably form the radical dication and fluoroethane upon interaction with Selectfluor (Scheme 7.5). To our satisfaction, adding a catalytic amount of triethylborane to a solution of Selectfluor and cyclododecane in MeCN, with no measures taken to remove O_2, resulted in the formation of 1-fluorocyclododecane in 50% yield after 4 h. The involvement of ethyl radicals in initiating the reaction is supported by detection of fluoroethane by ^{19}F NMR. Furthermore, a few other synthetic methods have been published since our original copper system that effect an analogous fluorination reaction using catalytic amounts of iron,[114] vanadium,[151] and organic-based reagents[303] that conceivably participate in inner-sphere electron transfer chemistry with Selectfluor. (Note that other methods have also been published recently using photocatalysts that likely operate under much different initiation mechanisms.[152])

[151] Xia, J-B.; Ma, Y.; Chen, C. *Org. Chem. Front.* **2014,** *1*, 468-472.
[152] For examples: (a) Bloom, S.; Knippel, J. L.; Lectka, T. *Chem. Sci.* **2014,** *5*, 1175-1178. (b) Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C-H. *Chem. Commun.* **2014,** DOI: 10.1039/C4CC01848F. (c) Xia, J-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013,** *135*, 17494-17500.

Scheme 7.5. Alkane fluorination promoted by triethylborane



Additional efforts were made to probe the role of copper as an initiator by attempting to remove or sequester copper during the course of the reaction and also suggest the reaction does not need copper to proceed beyond initiation (see supporting information for details). Lastly, an experiment probing the potential for asymmetric induction - using a chiral variant of our bis(imine) ligand (derived from *trans* 1,2-cyclohexanediamine)[153] and the Mosher ester of 3-phenylpropanol[154] (as benzylic fluorination of this substrate establishes spectroscopically distinct diastereomers by ^{19}F NMR)[155] - resulted in a distribution of fluorinated products that was identical to the distribution when an achiral ligand was employed. In a small way, this helps support the notion that fluorine may not be transferred from a copper catalyst. All things considered, the evidence overwhelmingly insinuates

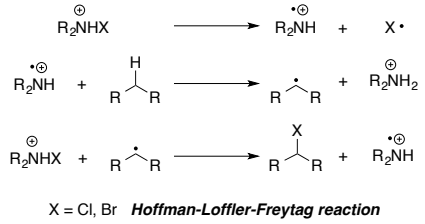
[153] For some applications of *N,N'*-bis(2,6-dichlorobenzylidene)cyclohexane-1,2-diamine in asymmetric catalysis, see: (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993,** *34*, 7027-7030. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993,** *115*, 5326-5327. (c) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010,** *12*, 2112-2115.

[154] The Mosher ester, 3-phenylpropyl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, was synthesized via standard DCC coupling chemistry. See: Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978,** *17*, 522–524.

[155] (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973,** *95*, 512-519. (b) Gorkom, M. v.; Hall, G. E. *Quart. Rev. Chem. Soc.* **1968,** *22*, 14-29.

that copper(I) is, in fact, an initiator in our system that operates through an inner-sphere electron transfer mechanism with Selectfluor, as opposed to being necessary throughout the catalytic cycle.

Scheme 7.6. Radical cation involvement in the Hoffman-Löffler-Freytag reaction



As suggested in Scheme 7.4, copper(I) is used to generate what we propose to be the true "catalyst" from Selectfluor – a radical dication.[156] Conceptually, if this radical dication acts as an H-atom abstractor, an alkyl radical would be generated that could feasibly react with Selectfluor to form the fluorinated product and regenerate the radical dication. This idea is akin to the mechanism established by Corey and co-workers for the Hoffman-Löffler-Freytag reaction (Scheme 7.6).[157] Correspondingly, the next set of experiments discussed focus on probing the involvement of radicals.

[156] Radical dication was observed by UV-Vis spectroscopy in a spectroelectrochemical experiment (procedure described in supporting information) whereby the corresponding amine, 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octan-1-ium tetrafluoroborate, is oxidized in MeCN via controlled potential electrolysis. Over 1 h, a new absorbance grew in at 273 nm. It is impossible to observe this absorbance under the normal reaction conditions/concentrations.
[157] For example: Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960,** *82*, 1657-1668.

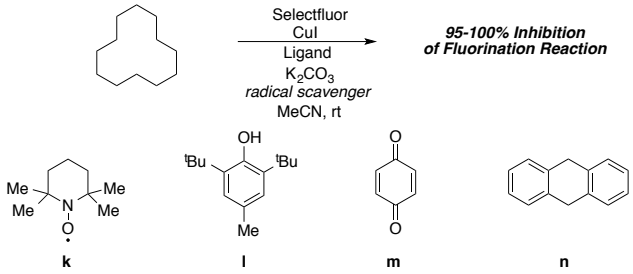
7.6) INVOLVEMENT OF ALKYL RADICALS

The reaction was run in the presence of four radical scavengers to explore the involvement of radical intermediates: 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) **k**, 2,6-di-*tert*-butyl-4-methylphenol (BHT) **l**, *p*-quinone **m**, and dihydroanthracene **n** (Scheme 7.7).[158] Subjecting cyclododecane to normal reaction conditions with an added 1.2 equiv. of each radical scavenger, the formation of fluorocyclododecane was inhibited by 95% in the presence of *p*-quinone, 97% with BHT, and completely in the presence of either TEMPO or dihydroanthracene. One potential criticism of these experiments may be that some of these compounds do not solely act as radical scavengers; rather, some will likely also be fluorinated or oxidized, consuming a significant amount of Selectfluor, and thus inhibiting fluorination through another venue. To elucidate the primary role of these compounds as radical inhibitors, we also found that 1) merely 0.15 equiv. of TEMPO and dihydroanthracene - leaving a fifteen-fold excess of Selectfluor - also resulted in significant reaction inhibition (85% with TEMPO and 70% with dihydroanthracene) without any substantial amount of fluorinated variants of the scavengers detected and 2) if dihydroanthracene is added at any point after fluorinated products start to appear by ^{19}F NMR, the fluorination reaction stops. These experiments strongly infer the shutting down of

[158] Save the experiment with dihydroanthracene, a similar study was done in: Vincent, S. P.; Burkart, M. D.; Tsai, C-Y.; Zhang, Z.; Wong, C-H. *J. Org. Chem.* **1999,** *64*, 5264-5279.

a radical pathway. Note that oxygen also quenches the reaction – typical of many radical chain reactions.

Scheme 7.7. Fluorination reaction in the presence of radical scavengers



Although we have shown the ability to interrupt the proposed radical pathway, these experiments do not necessarily allude to the scavenging of *alkyl* radicals. In fact, the aforementioned compounds and oxygen are likely to inhibit the reaction via cessation of the radical dication. The best way to probe the involvement of alkyl radicals is to run the reaction with substrates that notoriously rearrange to provide more stable radicals or release ring strain, such as those containing a cyclopropyl moiety. The rates of rearrangement have been studied for several "radical clocks," and under certain circumstances allow the possibility of extrapolating rate information from the reaction. We studied a small family of cyclopropane-based radical clocks, spanning rearrangement rates over a few orders of magnitude (Table 7.2).

The first three radical clocks studied – benzylcyclopropane, thujone, and norcarane[159] – showed evidence of fluorinated product mixtures by ^{19}F NMR, but no detectable amount of the expected "rearranged" fluorinated products following the putative formation of radicals **o**, **p**, and **q**, respectively.[160] However, the rate of fluorination may be significantly faster than their rates of rearrangement, and the latter two clocks have multiple competing sites for H-atom abstraction that would not allow for a rearranged product anyway. Accordingly, we examined another slightly faster clock with one favorable benzylic site for H-atom abstraction under our reaction conditions – 2-phenylbenzylcyclopropane (to form radical **r**).[161] A ^{19}F NMR analysis revealed that the reaction yielded four fluorinated products in a total yield of 18.2% – one of these signals corresponds to the (*E*)-isomer of rearranged product **s** (d = -172.53 ppm, ddd, *J* = 47.4, 24.8, 16.5 Hz) and another signal also has the characteristics of an "opened" fluorinated clock (d = -178.69 ppm, ddd, *J* = 48.5, 39.2, 14.4 Hz).[162] The two additional signals have slightly more difficult splitting to decipher, but have chemical shifts that reasonably match up with two benzylic fluorinated isomers

[159] Benzylcyclopropane and norcarane were synthesized according to literature procedure. See: Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959,** *81*, 4256-4264.

[160] For respective rates of rearrangement of benzylcyclopropane, thujone, and norcarane, see: (a) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991,** *113*, 5699-5707. (b) He, X.; Ortiz de Montellano, P. R. *J. Org. Chem.* **2004,** *69*, 5684-5689. (c) Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* **2002,** *124*, 6020-6027.

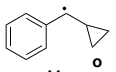
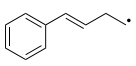
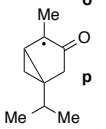
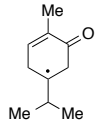
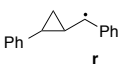
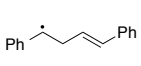
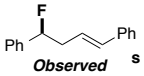
[161] 2-Phenylbenzylcyclopropane was synthesized according to literature procedure. See: Aguila, M. J. B.; Badiei, Y. M.; Warren, T. H. *J. Am. Chem. Soc.* **2013,** *135*, 9399-9406. For rate of rearrangement, see: Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992,** *57,* 4284–4287.

[162] Although it is difficult to isolate the low-yielding products under the reaction conditions, we confirmed the presence of the (*E*)-isomer in the reaction mixture by synthesizing each isomer by other means and comparing ^{19}F NMR shifts, splitting, and coupling constants.

that contain an intact cyclopropane ring (d = -179.81 ppm, m and d = -185.33 ppm, m). The identification of these compounds is also supported by a crude GC/MS analysis where four similar fragmentation patterns were found with *m/z* = 226.3. The ratio of total rearranged products to intact cyclopropane products is ca. 1:1.09. This rearrangement is strong evidence for a stepwise fluorination mechanistic pathway and for the involvement of short-lived alkyl radicals.

As an aside, the fact that the reported rates of rearrangement for norcarane and 2-phenylbenzylcyclopropane are very similar, yet we found no rearranged norcarane products, is a noteworthy result. As either rearrangement or fluorination of the radical happens *after* the rate-determining step (*vide infra*), this observation indicates that secondary alkyl radicals fluorinate faster than the more delocalized secondary benzylic radicals in this reaction.

Table 7.2. Radical clocks.

	Rearrangement		*Rearranged Fluorinated Product*
 **o**	$k_r < 2.0 \times 10^5\ s^{-1}$		*Not observed*
 **p**	$k_r \sim 1.0 \times 10^8\ s^{-1}$		*Not observed*
 **q**	$k_r = 2.0 \times 10^8\ s^{-1}$		*Not observed*
 **r**	$k_r = 3.6 \times 10^8\ s^{-1}$		 ***Observed*** **s**

Thus far, these experiments paint a reasonably convincing picture where a radical dication generates an alkyl radical, which may react homolytically with

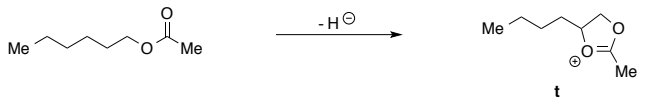
Selectfluor to yield a fluorinated product and regenerate the radical dication. One alternative to consider is the role that carbocations may play in the mechanism, as cationic intermediates may also result in the opening of the cyclopropane ring. For example, can an alkyl radical sacrifice another electron to a suitable acceptor and then trap fluoride? There are a number of factors from theoretical and experimental standpoints that militate against this possibility. Most of all, we would be considering secondary cations, whose free existence in solution is at the very least unfavorable, and somewhat debatable.[163] In any case, a secondary cation in MeCN solvent would rapidly collapse to the nitrilium as opposed to trapping fluoride. Nitrilium adducts – rather, acetamides upon aqueous workup – were observed by Baran and co-workers in a copper(II)-Selectfluor based system.[130] However, their postulated mechanism, involving a copper(II) reagent that is subjected to harsher conditions in the presence of Selectfluor, invokes formation of a precedented copper(III) species that is much more likely to be reduced by an alkyl radical than our observed copper(II) species (Scheme 7.8). The fact that nitrilium derived products are minimal in our system (aside from *ex post facto* solvolysis) would seem to indicate that cations play a minor role.

[163] Hydrido-bridged secondary cations are considered more stable, viable intermediates in solution. For direct observation of this phenomenon with secondary cycloalkane cations, see: Kirchen, R. P.; Sorensen, T. S. *J. Am. Chem. Soc.* **1979,** *101*, 3240-3243.

Scheme 7.8. Nitrilium formation in copper(III) promoted C-H functionalization

What about direct formation of cations through hydride transfer? Take the well-behaved substrate 1-hexyl acetate, which fluorinates predominately in the 5-position, as a model. Hexyl acetate should donate hydride preferentially from the 2-position, as this would form, after anchimeric assistance, a stable cyclic oxonium **t** that could trap fluoride (Scheme 7.9). This product is not observed to any significant extent.

Scheme 7.9. Formation of oxonium cation from 1-hexyl acetate



7.7) INDUCTION PERIOD

A mechanistic study would not be complete without an analysis of reaction kinetics. A preliminary kinetic study to monitor the rate of appearance of the fluorinated product of 3-phenylpropyl acetate by ^{19}F NMR under standard reaction conditions revealed a significant induction period before the desired 3-fluoro-3-phenylpropyl acetate began to form. Over the course of our studies,

we have noted induction periods for this same compound varying anywhere from 20 min to 2.5 h. We also found that the length of this induction period can vary greatly among all substrates; for instance, the induction periods for monitored reactions with cyclodecane or cyclohexane have varied in length on the orders of minutes to hours, just as 3-phenylpropyl acetate has. (A sample plot of the rate of fluorination of cyclodecane is provided below, illustrating the induction period (Figure 7.7).)

To determine whether the substrate itself plays a significant role in the induction period of the reaction, we looked at the consequences of "aging" the catalyst in six reactions set up in parallel. In this experiment, 3-phenylpropyl acetate was added at six different time intervals (t = 0, 15 min, 30 min, 1 h, 2 h, and 4 h) into six different reaction flasks, and an aliquot was taken from each flask at the 4.5 h mark. In every instance where the starting material was added at/prior to 2 h, the percent yields of the fluorinated products by ^{19}F NMR relative to an internal standard were virtually identical. However, in the reaction where the starting material was added at 4 h, well past any previously observed induction period, the fluorinated product had already appeared after only 30 min of stirring, and in half the percent yield of the other reactions. Thus, the induction period does not appear to be substrate dependent.

We noticed shorter induction periods as technique improved, presumably with respect to excluding oxygen from the system. In fact, suspecting the involvement of radical species, we noted that the reaction is greatly hindered in the presence

of an O_2 atmosphere and also found that the induction period is typically shorter using degassed anhydrous MeCN (with N_2) over simply anhydrous MeCN (with no measures taken to remove dissolved oxygen).[164] If oxygen is quenching the radical dication, then the origin of the induction period is likely attributed to a slower build-up in concentration of radical dication, the effective catalyst, *in situ*.[165] Even after rigorous efforts to exclude oxygen, a small concentration was present in each reaction – the induction periods shortened significantly, but never disappeared.

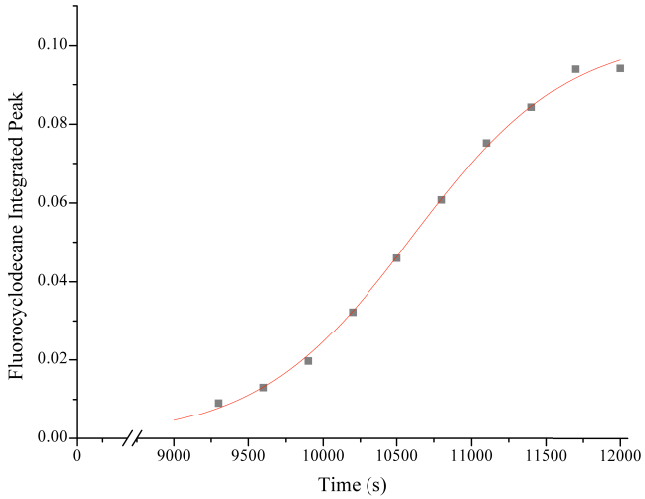


Figure 7.7. Sample rate of fluorination plot displaying induction period.

[164] For some examples of oxygen consumption causing induction periods and retarding reaction rates in radical processes, see: (a) Cunningham, M. F.; Geramita, K.; Ma, J. W. *Polymer* **2000,** *41*, 5385-5392. (b) Okubo, M., Ed. *Polymer Particles (Advances in Polymer Science*); Springer-Verlag Berlin Heidelberg: The Netherlands, 2010.

[165] For some examples of induction period dependences on catalyst concentration, see: (a) Singh, U. K.; Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124*, 14104-14114. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002,** *124*, 390-391. (c) Márta, F.; Boga, E.; Matók, M. *Discuss. Faraday Soc.* **1968,** *46*, 173-183.

7.8) RATE DEPENDENCE

We next sought to determine the overall order of the reaction using the method of initial rates; however, it is very challenging if not impossible to obtain quantitative rate dependencies for this reaction, given its induction period and the limited solubility of several components.

Our model thus far involves three steps: 1) an inner-sphere SET event between Selectfluor and copper(I) generates copper(II) and a radical dication; 2) this radical dication performs H-atom abstraction on an alkane, which generates an ammonium salt and an alkyl radical; and 3) the resultant alkyl radical abstracts a fluorine atom from Selectfluor, which regenerates the radical dication to enter the catalytic cycle. Since the radical dication is believed to be the true catalyst (or chain carrier), and if H-atom abstraction is the rate-limiting step, the rate of product formation (studied by ^{19}F NMR) would likely have a first-order dependence on both the alkane and the radical dication. Our data show that the rate of product formation is, in fact, strictly first-order with respect to the substrate.

The rate of radical cation formation is dependent on the concentrations of copper(I) and Selectfluor, but the observed induction period seriously complicates the picture. Qualitatively, the length of the induction period is inversely proportional to the concentration of copper and proportional to the concentration of oxygen. We also observed that copper(I) is not entirely

expended as the reaction rate accelerates. The total concentration of radical cation, and thus product, is dependent on a first order term in Selectfluor and a reciprocal first order term (reflecting the production of the radical dication). An accurate mathematical analysis of the rate dependencies of Selectfluor and copper(I) is less feasible under these circumstances, but qualitatively they should both be < 1 (depending on the relative contributions of the two terms), which proved to be the case. The proposed rate equation is illustrated below (Eq. 7.1).

$$\frac{d[\text{fluoroalkane}]}{d[t]} = k[\text{alkane}][\text{radical dication}]$$
$$\frac{d[\text{radical dication}]}{d[t]} = k_1[\text{Selectfluor}][\text{Cu}] - k_2[\text{Selectfluor}][\text{Cu}][\text{quencher}] \quad (1)$$

Equation 7.1. Proposed rate equation

7.9) KIE

Kinetic isotope effect (KIE) experiments are also capable of providing a wealth of knowledge about a reaction mechanism, from information about the rate-determining step to intimate details about the nature of the transition state.[166] An appropriate benzylic substrate for this experiment would be 3-phenylpropyl acetate, as it yields only one fluorinated product (in the benzylic position) and the corresponding mono/dideutero species is easily accessible (**49-*d*$_1$** and **49-*d*$_2$**

[166] (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, **2006**. (b) Giagou, T.; Meyer, M. P. *Chem. Eur. J.* **2010,** *16*, 10616-10628.

respectivley).[167] The appearance of fluorinated products **50-*d*$_1$** and **50-*d*$_2$** was monitored by ^{19}F NMR in a competitive KIE experiment, as the deuterium-induced ^{19}F isotopic shift is significant enough to allow independent observation of the geminal protio- and deuterio- products (Dd = 0.59 ppm; Figure 7.8).[168] This method also obviates misleading results from potential inconsistencies in induction periods.

Comparison of the initial rates revealed an average kinetic isotope effect of 2.3, which is a superposition of a moderate primary KIE and a secondary effect from the dideuterio species (Scheme 7.10). This diminished putative primary KIE value appears to be consistent with an early or bent transition state if the rate-limiting step is, in fact, H-atom abstraction.[169] A transition state calculation of the radical dication engaging in H-atom abstraction at B3LYP/6-311^{++}G** supports this notion (d(C-H) = 1.17 Å, d(N-H) = 1.69 Å)). (In order to simplify the calculation, the aliphatic substrate used was propane. Counterions were included in an MeCN dielectric, as otherwise without counterions present the barrier to H-atom transfer diminished to zero).

A second competitive KIE experiment was also conducted using a purely aliphatic substrate, *viz.* a 1:1 mixture of cyclohexane: cyclohexane-d_{12}, which

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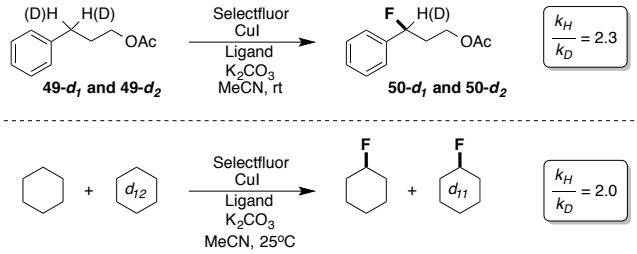
[167] Kurita, T.; Hattori, K.; Seki, S.; Mizumoto, T.; Aoki, F.; Yamada, Y.; Ikawa, K.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* **2008,** *14*, 664-673.

[168] For instance, see: Osten, H. J.; Jameson, C. J.; Craig, N. C. *J. Chem. Phys.* **1985,** *83*, 5434-5441.

[169] (a) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970,** 785-790. (b) Strong, H. L.; Brownawell, M. L.; San Filippo, Jr., J. *J. Am. Chem. Soc.* **1983,** *105*, 6526-6528. (c) Westheimer, F. H. *Chem. Rev.* **1961,** *61*, 265-273.

provided a slightly smaller average value of 2.0 (Scheme 7.10). Similar to the 3-phenylpropyl acetate result, there is a moderate primary isotope effect and small secondary effect from the geminal deuterium atom. On the other hand, cyclohexane-d_{12} has four vicinal deuterium atoms that have an inverse secondary effect on the rate that accounts for a notable diminution of the phenomenological KIE value.

Scheme 7.10. KIE experiments



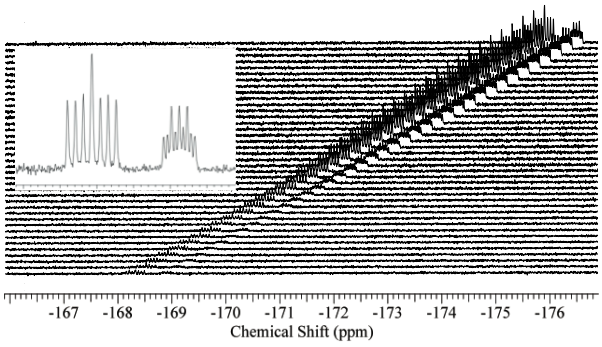
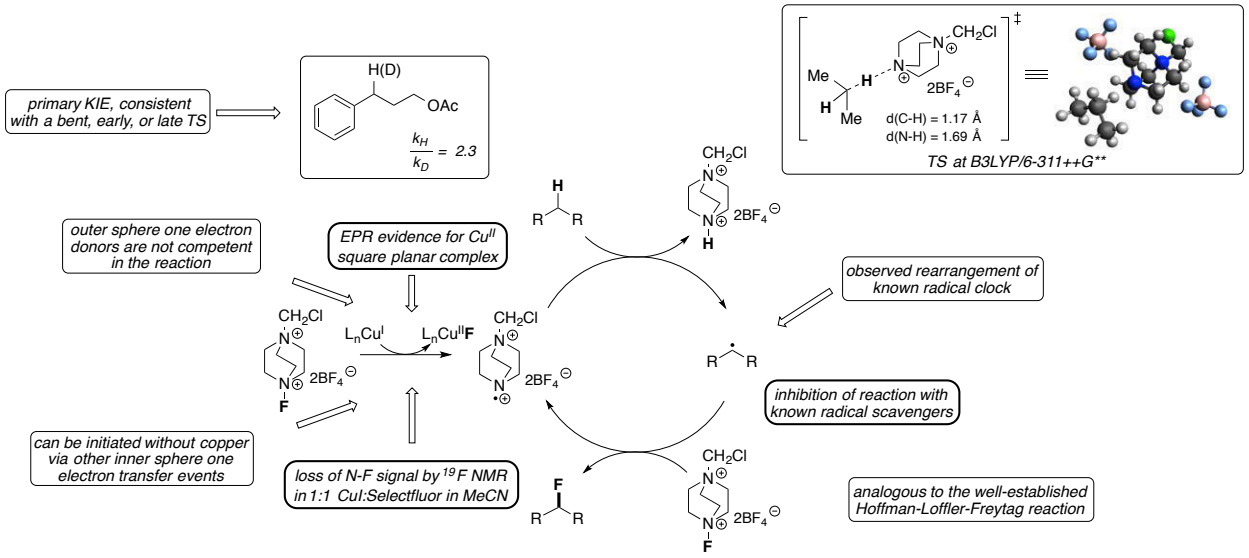


Figure 7.8. Competitive KIE ^{19}F NMR overlay of the formation of 3-fluoro-3-phenylpropyl acetate (*left*, ddd, J = 47.4, 30.9, 14.4 Hz) and 3-fluoro-3-phenylpropyl-3-*d* acetate (*right,* ddt, J = 30.9, 14.4, 7.2 Hz).

7.10) PROPOSED MECHANISM

Based on experimental observations thus far, we can propose a reasonable mechanism. EPR, UV-Vis, ^{19}F NMR, and several synthetic experiments point to an inner-sphere SET reaction between copper and Selectfluor whereby copper(I) is oxidized to copper(II) accompanying a loss in fluoride from Selectfluor. As determined by the aforementioned KIE experiments and transition state calculation, the resultant radical dication species from the SET reaction is a reasonable actor in H-atom abstraction that occurs through an early transition state and is postulated to be rate-determining. Radical scavenger and radical clock experiments confirm the involvement of alkyl radicals that would be formed along with ammonium salt (observed) upon H-atom abstraction. Furthermore, the notion that fluorine is being transferred directly from Selectfluor is logical, as this would regenerate the radical dication and complete a catalytic cycle/radical chain reaction similar to the Hoffman-Löffler-Freytag reaction (Figure 7.9).

Figure 7.9. Mechanistic hypothesis based on experimental results



We have also provided an energetic profile of the reaction intermediates in the catalytic cycle that illustrates a largely exothermic reaction pathway (Figure 7.10).

Overall, this picture appears to be a reasonable mechanism for this system. However, perhaps the most difficult question to answer pertaining to the selectivity of the reaction still remains: *why is monofluorination preferred?* Finally, we turned our attention to a more in-depth theoretical analysis to try to complete the puzzle.

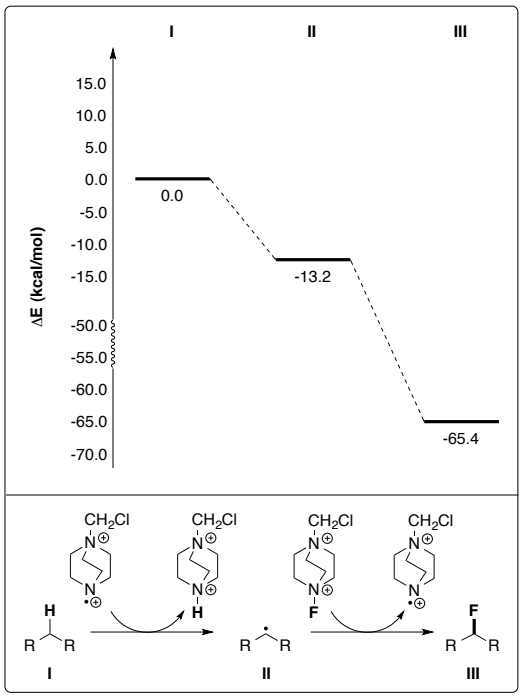


Figure 7.10. Free-energy profile for the monofluorination of cyclodecane through our proposed catalytic cycle.

7.11) ROLE OF VALENCE BOND "IONICITY" IN REACTION SELECTIVITY

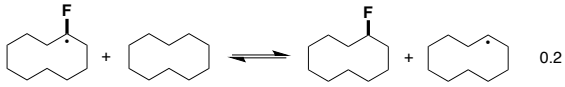
One of the most enlightening features regarding the selectivity of this reaction is in the highly reproducible product distribution of 1-hexyl acetate. Fluorination of this substrate predominates in the 5-position, yields of the other monofluorinated isomers largely decrease moving down the chain, and there are trace (if any) monofluorinated products in the 1-position, 6-position, and α-position to the carbonyl. Compare this to the outcome of a reaction using *n*-dodecane, where an almost equal distribution of monofluorinated products on

the methylene sites is observed. It is clear that the reaction is sensitive to substituent effects that will provide some potent clues.

From one vantage point, as we propose a mechanism involving a radical chain process, we conducted a computational experiment early on that interestingly suggested the observed distribution of *n*-fluoro-1-hexyl acetate isomers correlates with the calculated relative stabilities of the corresponding hexyl acetate radicals. If the selectivity of the reaction is based solely on radical stability though, which is characteristic of a purely covalent valence bond model for the rate-determining H-atom abstraction transition state,[170] then geminal difluorination should be favored. Also consider the isodesmic analyses of cyclohexane and cyclodecane (Table 7.3) that indicate favorable formations of 1,1-difluorocyclohexane and 1,1-difluorocyclodecane over monofluorination based on thermodynamic considerations; yet, *geminal difluorinated products are not observed experimentally,* except to a minor extent when we apply forcing conditions (but even then, ionization/trapping of acetonitrile is a more competitive process). The desire to analyze this reaction in terms of generating the most stable radical, a bond dissociation energy argument, is thus a misguided instinct.

[170] Hiberty, P. C.; Megret, C.; Song, L.; Wu, W.; Shaik, S. *J. Am. Chem. Soc.* **2006,** *128*, 2836-2843.

Table 7.3. Isodesmic reactions.

Isodesmic Reaction	*ΔE (kcal/mol)*
	0.8
	0.2

All geometry optimizations were performed at B3PW91/6-311+G**(MeCN).

Instead, if we revisit the substituent effect observed in 1-hexyl acetate as an effect resembling that of a radical reaction with *ionic* character in the transition state, then we can begin to rationalize the selectivity. In this light, the deactivation of sp^3 C-H sites proximal to an electron-withdrawing group toward fluorination agrees nicely with our proposed mechanism. The species we suggest is responsible for H-atom abstraction, a radical dication, is an electron deficient radical that would much prefer interaction with the more electron rich C-H sites (hence the starting material over the newly-formed fluorinated products).

7.12) POLAR EFFECT

Ionic-like selectivity is not unheard of in radical reactions; there are several accounts of this phenomenon in the literature, first noted by Walling and Mayo[171] in free radical polymerization reactions and since referred to as "the polar effect."

[171] See: C. Walling. "Free Radicals in Solution." Wiley: New York, N. Y., **1957**; pp. 132-140, 365-369, 375-376, 474-491.

By analogy of our reaction to the Hoffman-Löffler-Freytag reaction, reports demonstrating that this polar effect, putatively at play in our fluorination reaction, is similarly observed in free radical chlorination[172] and bromination[173] reactions involving intermolecular H-atom abstraction also by amine radical cations make an extremely convincing argument for our case. These reports also indicate an overwhelming preference for the penultimate sp^3 C-H site on *n*-alkyl esters, which they attribute to such polar (and also minor steric) effects.

The last piece of the puzzle lies in further examining the effect of ionicity on the H-atom abstraction transition states of the alkane versus the monofluorinated product. Postulating the role of the ionic potential energy surface on dictating selectivity and given the complexity of transition state calculations, we first turned to Donahue's seminal ionic curve crossing theory as a way to study the nature of the transition states – only geometry optimization calculations are necessary by this analysis.[174] This theory indicates that the lowering in energy of the saddle point on the ground state potential energy surface results from an avoided curve crossing with the ionic potential energy surface. Succinctly stated, lower ionic state energies correlate with lower transition state energies. Boundary conditions for an avoided curve crossing are derived from plotting the evolution of the ground and ionic state energies as reactants approach each other (bear in mind

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[172] (a) Minisci, F.; Galli, R.; Galli, A.; Bernardi, R. *Tetrahedron Lett.* **1967,** *23*, 2207-2209. (b) Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* **1968,** 324-325.
[173] Minisci, F.; Galli, R.; Bernardi, R. *Chem. Commun.* **1967,** 903-904.
[174] Donahue, N. M.; Clarke, J. S.; Anderson, J. G. *J. Phys. Chem. A* **1998,** *102*, 3923-3933.

that for radical cation abstraction reactions, the ground state is ionic, as well). In our system, DE_1 is the calculated difference between ground and "ionic" states of the reactants, DE_2 is the same for the products, DE_a is the activation energy, DH_{REACT} is the reaction enthalpy, and CP is the potential energy surface crossing point (Eq. 7.2).

$$CP = \frac{\Delta E_1(\Delta E_1 + \Delta H_{REACT})}{\Delta E_1 + \Delta E_2} \qquad (2)$$

Equation 7.2. Potential energy surface crossing point (CP) calculation

For cyclodecane, CP is calculated to be 4.6 kcal whereas fluorocyclodecane as a precursor to the more stable 1-fluorocyclodecyl radical, leads to CP = 5.4 kcal (B3PW91/6-311++G**/MeCN), implying a higher activation energy for its formation - consistently accounting for the observed selectivity from this reaction (Figure 7.11).

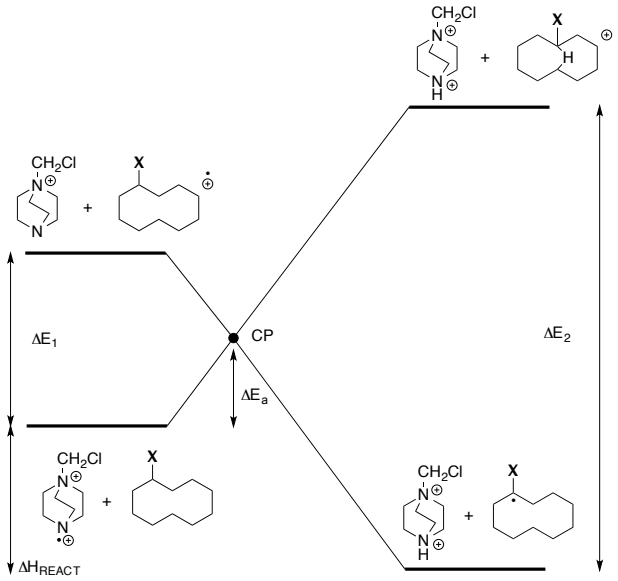


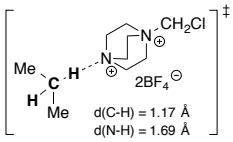
Figure 7.11. Application of Donahue's theory.

The calculations in Figure 7.11 include optimized geometries of the 1-fluorocyclodecyl and cyclodecyl cations, both of which are found to be hydrido-bridged employing the MeCN continuum. This model is consistent in predicting the observed preference for monofluorination of cyclohexane, as well. For cyclohexane, CP is calculated to be 3.4 kcal, which is a lower barrier than that of fluorocyclohexane at 5.5 kcal.

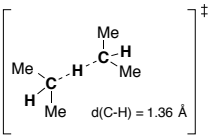
Additionally, we calculated the transition states for formation of the isopropyl radical and the 2-fluoro-isopropyl radical, representing pruned substrates for ease of calculation. The result is in excellent agreement with the curve crossing analysis *vide supra*, as the transition state for the formation of the isopropyl radical is earlier and calculated to be 2.2 kcal lower than for the formation of the 2-fluoro-isopropyl radical at B3LYP/6-311++G**. An NBO analysis also confirms

that a positive charge has developed in the transition state (relative to an isoenergetic H-atom abstraction) that is accentuated on the hydrogen atom. A strong electron-withdrawing group such as fluorine would destabilize this positive charge, advocating again for H-atom abstraction of an alkane over a fluoroalkane (Figure 7.12).

Finally, note that all attempts to calculate the transition state whereby Selectfluor fluorinates the isopropyl radical repeatedly collapsed to the products, potentially signifying a barrier-less reaction.

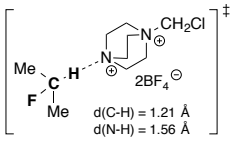


vs.

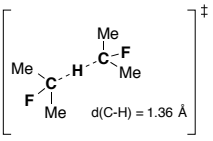


Atom	*Natural Charge (a.u.)*
H	0.216
C	-0.296
H	0.249

Atom	*Natural Charge (a.u.)*
H	0.179
C	-0.281
H	0.208



vs.



Atom	*Natural Charge (a.u.)*
F	-0.372
C	0.320
H	0.257

Atom	*Natural Charge (a.u.)*
F	-0.429
C	0.317
H	0.165

Figure 7.12. Transition state calculations and charge distributions alongside isoenergetic scenarios.

7.13) CONCLUDING REMARKS

Through in-depth analysis of experimental and theoretical data, we are able to propose a mechanistic scenario of the copper-initiated sp^3 C-H fluorination methodology. Spectroscopic evidence and synthetic experiments confirm a radical chain mechanism initiated by an inner-sphere SET from copper(I) to Selectfluor (as opposed to a mechanism where copper plays a role in the catalytic cycle), but this alone does not explain the observed preference for monofluorination. Analyzing the influence of the ionic potential energy surface and applying Donahue's ionic curve crossing theory has allowed us to offer a reasonable explanation for the energetics and selectivity of the reaction.

CHAPTER 8

A COOPERATIVE ALLYLIC FLUORINATION: COMBINATION OF NUCLEOPHILIC AND ELECTROPHILIC FLUORINE SOURCES

8.1) INTRODUCTION TO ALLYLIC FLUORINATION

The selective incorporation of fluorine has become a powerful strategy in the optimization of pharmaceuticals, [175] agrochemicals, [176] and performance materials. [177] The unique properties of the fluorine atom make it an ideal bioisostere for hydrogen or oxygen, while imparting a unique set of physical and chemical properties onto the parent molecule.[12,178] For instance, substitution of a single C–H bond with fluorine has been shown to enhance membrane permeability, metabolic stability, and binding affinities of potential drug candidates, among other notable features.[45,46,83] In addition, the ^{18}F radioisotope is ideally suited for use in positron emission tomography (PET) imaging due to its low-energy emission, ease of preparation from [^{18}O] water, and appreciable half-

[175] (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2013.** 131203141941007; (b) Filler, R.; Saha, R. *Future Med. Chem*. **2009,** *1*, 777–791; (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007,** *317*, 1881–1886.

[176] (a) Theodoridis, G. *Adv. Fluorine Sci*. **2006,** *2*, 121–175; (b) Key, B. D.; Howell, R. D.; Criddle, C. S. *Environ. Sci. Technol*. **1997,** *31*, 2445–2454; (c) Cartwright, D. *Organofluorine Chemistry: Recent Development in Fluorine-Containing Agrochemicals*; Springer: U.S., **1994**; pp 237–262.

[177] (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun*. **2007,** 1003– 1022; (b) Maienfisch, P.; Hall, R. G. *Chimia* **2004,** *58*, 93–99.

[178] (a) Bhatia, R.; Sharma, V.; Shrivastava, B.; Singla, R. K. *Pharmacology online* **2011,** *1*, 272–299.

life.[179] Accordingly, methods for the direct conversion of C–H to C–F bonds are of high synthetic value. While preparative methods for aryl fluorides[180] and α-fluorocarbonyl compounds[62,108,118,181] have advanced dramatically over the last decade, methods for the synthesis of allylic fluorides also remain in considerable demand. The allyl fluoride moiety is found in a variety of medicines and agrochemicals from common insecticides and herbicides to synthetically complex prostanoid analogues (Figure 8.1).[182] In addition to these cases, allylic fluorides serve as versatile building blocks in the construction of various fluorinated compounds.

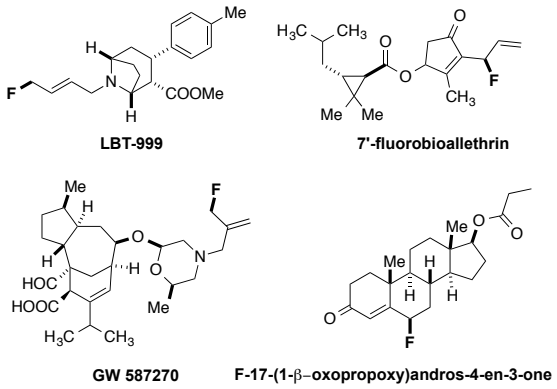


Figure 8.1. Allylic fluorides in medicine

[179] (a) Alauddin, M. M. Am. *J. Nucl. Med. Mol. Imaging* **2012,** *2*, 55–76; (b) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008,** *17*, 2853–2873; (c) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008,** *47*, 8998–9033.
[180] (a) Fier, P. S.; Luo, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013,** *135*, 2552–2559; (b) Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010,** *49*, 2219– 2222; (c) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010,** *11*, 1804–1821.
[181] Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011,** *133*, 1738–1741.
[182] Khan, M. O. F.; Lee, H. *J. Chem. Rev.* **2008,** *108*, 5131–5145.

Until recently, the synthesis of allylic fluorides has often relied heavily on the dehydroxylation of alcohols with (diethylamino)sulfur trifluoride[183] or nucleophilic fluorination of preassembled allylic halides, [184] *p*-nitrobenzoates, [185] trichloroacetimidates, [186] and phosphorothioates [187] catalyzed by an array of transition metals, most notably Pd, Ir, and Cu. However, these and corresponding methods often suffer from poor regioselectivity and narrow substrate scope, especially in the way of unactivated or sp^3-rich cyclic alkenes. It was our interest to devise a complementary system for the fluorination of unactivated cyclic and acyclic olefins under mild conditions in part to address the cyclic olefin problem.

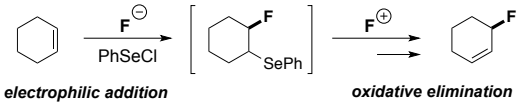
8.2) ALLYLIC FLUORINATION METHODOLGY

Previously, it has been reported that the use of ambiphilic fluorinating agents, or a combination of appropriate electrophilic and nucleophilic sources of fluorine, may be used to afford vicinal difluorides in excellent yields and selectivities from the starting alkene. [188] We envisaged a bicomponent system utilizing both fluorination strategies in which electrophilic addition is accompanied by an

[183] (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002,** *17*, 2561–2578; (b) Boukerb, A.; Greé, D.; Laabassi, M.; Greé, R. *J. Fluorine Chem*. **1998,** *88*, 23–27.
[184] (a) Hollingworth, C.; Hazari, A.; Hopkinson, M. N.; Tredwell, M.; Benedetto, E.; Huiban, M.; Gee, A. D.; Brown, J. M.; Gouverneur, V. *Angew. Chem., Int. Ed*. **2011,** *50*, 2613–2617; (b) Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc*. **2010,** *132*, 17402–17404.
[185] Topczewski, J. J.; Tewson, T. J.; Nguyen, H. M. *J. Am. Chem. Soc*. **2011,** *133*, 19318–19321.
[186] Lauer, A. M.; Wu, *J. Org. Lett*. **2012,** *14*, 5138–5141.
[187] Zhang, Z.; Wang, F.; Mu, X.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed*. **2013,** *52*, 7549–7553.
[188] (a) Quan, H.-D.; Sekiya, A.; Tamura, M. *Eur. J. Org. Chem*. **1999,** *11*, 3151–3153; (b) Visser, G. W. M.; Bakker, C. N. M.; Halteren, R. W. V.; Herscheld, J. D. M.; Brinkman, G. A.; Hoekstra, A. *Recl. Trav. Chim. Pays-Bas* **1986,** *105*, 214–219; (c) Olah, G. A.; Welsch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekus, I.; Olah, J. A. *J. Org. Chem*. **1979,** *44*, 3872–3881.

oxidative elimination rather than nucleophilic trapping with fluoride to yield allylic products instead of a vicinal dihalide (Scheme 8.1).

Scheme 8.1. Proposed pathway for allylic fluorination



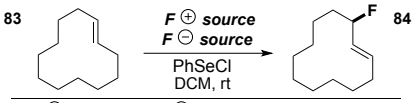
Toward this effort, it is well documented that PhSeF, generated *in situ* by the reaction of phenylselenyl chloride with silver(I) fluoride, adds regioselectively to alkenes to afford β-fluoro phenylselenides.[189] Moreover, electrophilic *N*–F reagents have been shown to oxidize both sulfur and selenium efficiently, often promoting their substitution or elimination with various nucleophiles and bases.[44,190] We surmised that the combination of PhSeF and an appropriate *N*–F reagent could be used in tandem to yield allylic fluorides from alkenes in a single reaction. It was therefore our idea to employ a tandem fluoroselenation–deselenation process mediated by phenylselenium fluoride and an electrophilic fluorinating agent, *N*-fluoropyridinium tetrafluoroborate (NFPy*BF_4), for the allylic fluorination of alkenes in a single reaction vessel without need for purification of the intermediate β-fluoroselenide.

To begin our studies, we selected the aliphatic alkene cyclododecene **83** as a prototypical substrate. During our initial screening, we surveyed a number of

[189] Barney, C. L.; Mathews, D. P.; McCarthy, J. R. *Tetrahedron Lett.* **1990,** *31*, 973– 976.
[190] (a) Kirihara, M.; Naito, S.; Ishisuko, Y.; Hanai, H.; Noguchi, T. *Tetrahedron Lett.* **2011,** *52*, 3086–3089.

electrophilic *N*–F reagents for reactivity including *N*-fluorobenzenesulfonamide (NFSI), Selectfluor, *p*-toluenesulfonylfluoride (TsF), and *N*-fluoropyridinium tetrafluoroborate in combination with cyclododecene, PhSeCl, and silver(I) fluoride in CH_2Cl_2 (Table 8.1). Among these reagents, NFPy*BF_4 performed most admirably, yielding 1-fluoro-2-cyclododecene (**84**) in 71% yield after 24 h.

Table 8.1. Screening of reaction conditions for allylic fluorination



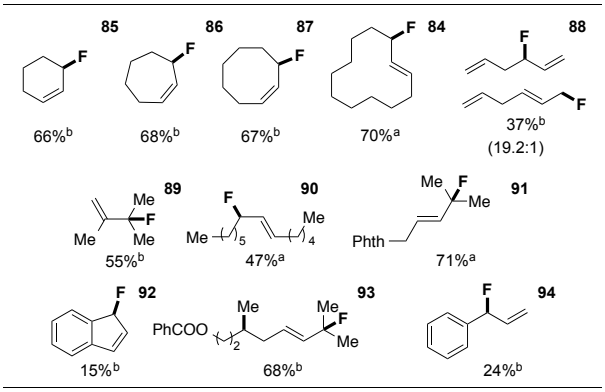
F ⊖ source	*F ⊕ source*	*yield %*
$NEt_3 \cdot 3HF$	Selectfluor	0
Py · HF	Selectfluor	0
TBAF	Selectfluor	0
Xtalfluor	Selectfluor	0
DAST	Selectfluor	14
AgF	Selectfluor	27
AgF	NFSI	0
AgF	TsF	0
AgF	NFPy · BF_4	71

Reactions were performed with PhSeCl (1.2 equiv), F^+ (2.2 equiv) and F^- (3.0 equiv) in CH_2Cl_2 (3 ml) over 24 h. Yields were determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard.

Note that the use of other nucleophilic fluoride sources failed to give any appreciable amount of the fluorinated product. Unsurprisingly, in the absence of AgF, NFPy*BF_4, or PhSeCl, no fluorinated products were observed. Attempts to optimize our system found that use of AgF (3.0 equiv), PhSeCl (1.2 equiv) and non-substituted NFPy*BF_4 (2.2 equiv) in DCM provided the best results. Gratifyingly, these reaction conditions proved amendable to cyclic, branched, and linear alkenes (Table 7.2). Of importance to note: (1) fluorination occurs at the most substituted carbon of the alkene; (2) allylic fluorides are favored over vinylic

fluorides; (3) monofluorination is preferred (of particular significance in the case of diene **88**; (4) the formation of rearranged products is minimal despite the possible participation of carbocations.

Table 8.2. Survey of allylic fluorinated products



All reactions were performed under an inert atmosphere of N_2 and stirred for 24 h (a) Isolated as the major fluorinated product. (b) Yield based on ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard.

Investigating further, we next examined monoterpenes as potential candidates for allylic fluorination. Isoprene-derived substrates are often valuable precursors in the biosynthesis of other, higher-order products and have found considerable applications as both flavor additives and fragrance enhancers.[191] We found that reaction of a hemiterpene under standard fluorination conditions afforded the tertiary fluoride **89** in 55% yield by ^{19}F NMR. Fortuitously, fluorinated analogues of a phthalimide **91** and biologically active citronellol benzoate **93** could be prepared equally as well.

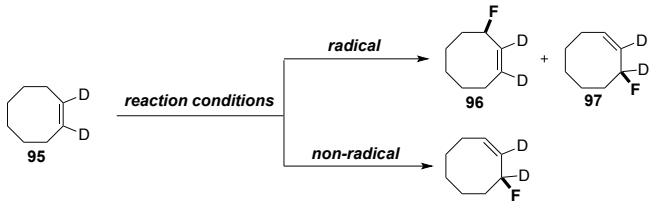
[191] Breitmaier, E. *Terpenes: Flavors, Fragrances, Pharmaca, Pheromones*; John Wiley & Sons, **2006**.

8.3) MECHANISTIC INSIGHT

Finally, we decided to undertake some preliminary mechanistic experiments. A reasonable place to start would be to assess the involvement of radicals–or equally likely–the participation of ionic intermediates (Scheme 8.2). In doing so, we sought the use of a vicinal dideuterated cycloalkene, d_2-1,2-cyclooctene **95**, as a mechanistic probe. If the reaction was to involve allylic radicals, we should obtain a mixture of labeled fluorides **96** and **97**. In contrast, if the reaction proceeds by a purely electrophilic pathway, that is, involving the formation of ionic intermediates, only **97** is expected. The identity of these products may readily be determined from a combination of ^{2}H NMR and ^{19}F NMR analyses. Experimentally, subjection of **95** to our reaction conditions provided a mixture of fluoroalkenes **96** and **97** in a 1:4 ratio suggesting the formation of radicals during the reaction. We postulate that the formation of radicals may be due to a high-valent silver fluoride generated *in situ*, as they are known to participate in radical-based fluorinations.[192] In fact, in the presence of only silver(II) fluoride, we found that trace quantities of **87** could be prepared from the starting alkene prompting further investigation.

[192] . (a) Mizuta, S.; Stenhagen, I. S. R.; O'Duill, M.; Wolstenhulmn, J.; Kirjavainen, A. K.; Forsback, S. J.; Tredwell, M.; Sandford, G.; Moore, P. R.; Huiban, M.; Luthra, S. K.; Passchier, J.; Solin, O.; Gouverneur, V. *Org. Lett.* **2013,** *15*, 2648–2651; (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012,** *134*, 10401–10404; (c) Durie, A. J.; Slawin, A. M. Z.; Lebl, T.; O'Hagen, D. *Angew. Chem*. **2012,** *124*, 10233–10235; (d) Zweig, Z.; Fischer, R. G.; Lancaster, J. E. *J. Org. Chem.* **1980,** *45*, 3597–3603.

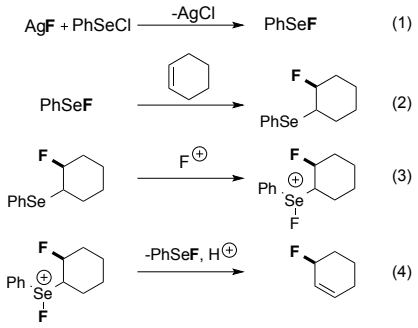
Scheme 8.2. Isotopic labeling study



To gain a more complete picture of the mechanism, we wanted to examine if β-fluoroselenides could be directly converted to allylic fluorides through reaction with NFPy*BF_4. To do so, the β-fluoroselenide, (2-fluorocyclooctyl) (phenyl)selenane was first prepared *in situ* by the reaction of *cis*-cyclooctene with silver(I) fluoride (3.0 equiv) and phenylselenyl chloride (1.2 equiv) in CH_2Cl_2. After stirring for 1 h, a crude ^{19}F NMR of the reaction mixture was obtained followed by the addition of NFPy*BF_4 (2.2 equiv). At this point, the reaction mixture was stirred for an additional 1 h, after which a second ^{19}F NMR spectrum was collected. Upon analysis, we found that after 1 h. no allylic products were evident. Instead, the only product we observed was fluoroselenide (12% yield). However, the inclusion of NFPy*BF_4 resulted in a mixture of allylic fluoride (8 % yield), and fluoroselenide (36% yield) along with a considerable buildup of HF. Clearly, NFPy*BF_4 is needed for product formation. In line with our findings, we propose the following tentative mechanism for the preponderant ionic pathway of the reaction (Scheme 8.3): (1) *in situ* formation of phenylselenium fluoride (PhSeF); (2) electrophilic addition of PhSeF to the alkene; (3) oxidation of selenium by NFPy*BF_4; and (4) elimination of phenylselenium fluoride to give the

allylic fluoride.

Scheme 8.3. Tentative mechanism for the ionic component of allylic fluorination



8.4) CONCLUDING REMARKS

In conclusion, a mild, cooperative protocol for the regioselective allylic fluorination of alkenes has been developed utilizing both electrophilic and nucleophilic sources of fluorine. This new system provides access to allylic fluorides over a precedent background vicinal difluoride. Preliminary mechanistic evidence suggests the involvement of both carbocations and radicals in the reaction, although their exact roles are not yet known. Continued efforts to discern the precise mechanism of this new reaction will be made, in addition to the search for new applications of our system to chemical synthesis and the construction of complex fluorinated molecules.

CHAPTER 9

A PHOTOCATALYZED ALIPHATIC FLUORINATION

9.1) INTRODUCTION TO PHOTOCATALYSIS

Although highly desirable, selective methods for the direct functionalization of simple hydrocarbons remain limited, often requiring the use of strong or poorly selective reagents (e.g. transition metal oxo complexes, *N*-oxo radicals, or organic peroxides).[193] Recently, it has been shown that the excited states of certain organic molecules can act as sufficient one-electron oxidants for the selective cleavage of (sp^3 C)–H bonds. [194] For example, 1,2,4,5-tetracyanobenzene (TCB), when sensitized by ultraviolet light ($\lambda_{max} \sim 266$ nm), is known to remove an electron from alkanes.[195] The resultant radical cations are very acidic and ephemeral species, presumably rapidly yielding alkyl radicals in turn. As such, adamantane radical cation affords the corresponding 1-yl, which then alkylates TCB itself.[193,194] Unsurprisingly, if an electrophilic fluorinating agent were present, fluorination could occur preferentially if the reagent were

[193] For recent reviews on alkane functionalization see: (a) Bergman, R. G. *Nature*, **2007,** *446*, 391–393. (b) Crabtree, R. H. *J. Chem. Organometal.*, **2004,** *689*, 4083–4091. (c) Jia, C,; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.*, **2001,** *34*, 633–639 (d) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.*, **1998,** *37*, 2180–2192.

[194] (a) Christl, M.; Braun, M.; Deeg, O. *Org. Biomol. Chem.,* **2013,** *11*, 2811–2817. (b) Mella, M.; Fagnoni, M.; Freccero, M.; Fasani, E.; Albini, A. *Chem. Soc. Rev.*, **1998,** *27*, 81–89. (c) Mella, M.; Freccero, M.; Albini, A. *Tetrahedron* **1996,** *52*, 5549–5562.

[195] (a) Protti, S.; Fagnoni, M.; Monti, S.; Rehault, J.; Poizat, O.; Albini, A. *RSC Adv.*, **2012,** *2*, 1897–1904. (b) Fokin, A. A.; Gunchenko, P. A.; Peleshanko, S. A.; von Ragu´e Schleyer, P.; Schreiner, P. R. *Eur. J. Org. Chem.*, **1999,** 855–860 (c) Mella, M.; Freccero, M.; Albini, A. *J. Chem. Soc., Chem. Commun.*, **1995,** *1*, 41–42.

more active than the rebounding TCB. Sammis et al., in pioneering work, have shown that alkyl radicals can in fact be efficiently fluorinated by electrophilic reagents, especially *N*-fluoro-*N*,*N*-bis(phenyl-sulfonimide).[87] More recently, fluorination of alkyl radicals by Selectfluor has been demonstrated by Li et al.,[196] and Inoue et al.[113c] under catalytic conditions. It was our idea to use catalytic TCB and UV light in conjunction with Selectfluor, an easy-to-handle, commercially available source of electrophilic fluorine for the fluorination of aliphatic and related systems (Figure 8.1).

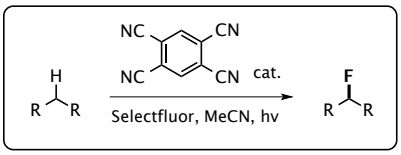


Figure 9.1. Photocatalyzed aliphatic fluorination

9.2) PHOTOCATALYZED METHODOLOGY

The value of organofluorine compounds to all branches of chemistry has increased exponentially over the past decade, from pharmaceutical science[197] to materials development[198] and synthesis.[199,200] Attending this explosive increase in scientific importance has been the quest to develop mild methods of

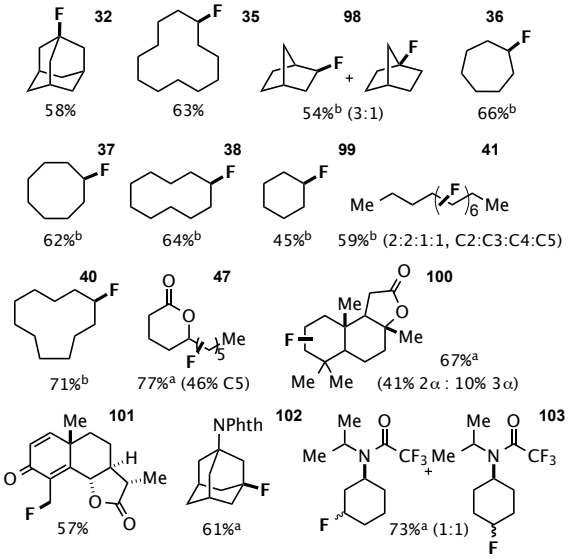
[196] Yin, F.; Li, Z.; Li, C. *J. Am. Chem. Soc*. **2012,** *134*, 10401– 10404.
[197] Filler, R.; Saha, R. *Future Med. Chem*. **2009,** *1*, 777–791.
[198] Maiensch, P.; Hall, R. G. *Chimia* **2004,** *58*, 93–99.
[199] Kitazume, T. *J. Fluorine Chem*. **2000,** *105*, 265–278.
[200] Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005,** *44*, 214–231.

fluorination, which are usually subdivided into two main areas wherein the fluorine atom acts as either an electrophile or a nucleophile.[201] Electrophilic fluorination, especially that involving C–H bond functionalization, has been historically characterized by the use of potentially dangerous, high energy reagents such as F_2 gas,[88] the explosive solid $CsSO_4F$,[90] and CoF_3,[23,89] which acts at high temperatures to afford polyfluorinated products. Paradoxically, although C–F bonds are strong (>100 kcal mol^{-1}), energetic reagents have been historically needed to form them. Recently, an active and timely area of interest has been the development of mild methods for aliphatic fluorination. These have unsurprisingly involved catalysis: the work of Groves, using Mn(porphyrin) complexes,[104] and our work using copper catalysis.[103] We thought it would be of interest to devise a simple, complementary procedure that obviated the use of transition metals yet could produce products in high yields and selectivities. Toward this effort, a new approach to the catalysis of alkane fluorination has been achieved by our laboratory employing ultraviolet light and 1,2,4,5-tetracyanobenzene (TCB) as a photosensitizer. This system overcomes the high oxidation potential of alkanes by way of a photoinduced electron transfer providing direct access to putative alkyl radicals that may be readily fluorinated in the presence of an electrophilic fluorinating reagent, Selectfluor. Ideally, radical cation formation is followed by fast loss of a proton to solvent (acetonitrile)

[201] For a review of selected fluorination methods see: (a) Kirk, K. L. *Org. Process Res. Dev*. **2008,** *12*, 305–321. (b) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev*. **2008,** *11*, 803–819. (c) Kirihara, M. *Yakugaku Zasshi* **2000,** *120*, 339–351. (d) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl*. **1981,** *20*, 647–667.

producing the radical, which can then be readily fluorinated.

Table 9.1. Survey of fluorinated alkanes



All reactions were performed under an inert atmosphere of N_2 and irradiated at 302 nm for 16 h (a) Isolated as the major fluorinated product with minor fluorinated isomers (b) Yield based on ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard.

The reaction system consists of a simple UV lamp, a water bath, and a culture tube containing the reagents under an inert atmosphere of N_2. The first substrate examined for screening purposes was cyclododecane **34**, as all C–H bonds are equivalent and the product mono-fluoride can be easily isolated and characterized. At the onset, cyclododecane proved to be a propitious choice for screening; it mono-fluorinates preferentially, affording fluorocyclododecane **35** in 63% yield. Gratifyingly, only trace amounts (at most) of the arylated alkane were identified. Although reactions were performed over 16 h, the majority of aliphatic

substrates were completely converted within 6 h by TLC and/or monitoring by ^{19}F NMR.

A working hypothesis for the mechanism of the reaction is shown in Figure 9.2. Given precedent,[193,194] it is postulated that TCB sensitization is followed by radical cation formation, loss of a proton to solvent, fluorination of the resulting radical, and finally back-electron transfer from TCB to the ammonium radical cation, and proton transfer from solvent. TCB is thus regenerated, and can act again.

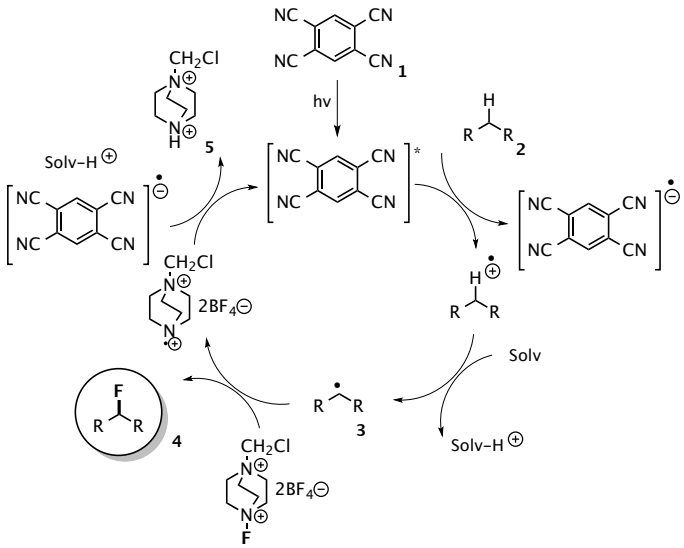


Figure 9.2. Working hypothesis for reaction mechanism

Examining a host of cyclic and linear alkanes, mono-fluorinated products were obtained in moderate to good yields and in fair selectivities (Table 9.1). In many instances, fluorination was found to occur at the carbon in accordance with relative radical stability. However, this is not always the case; whereas

adamantane reacts to afford 1-fluoroadamantane **32**, norbornane yields the methylene mono-fluoride predominantly **98**. Moreover, *n*-dodecane fluorinates considerably at C2 through C5, while minimally at C1 or C6 (**41**). It should be noted that for some substrates, particularly small cycloalkanes with a fair degree of strain energy, nonselective fluorination in the absence of photocatalyst was observed (<8%), a result consistent with Selectfluor's ability to act as a sufficient oxidant combined with the increased reactivity of strained alkanes. In such cases, it was found that use of *N*-fluoro-*N*,*N*-bis(phenylsulfonimide) or *N*-fluoropyridinium tetrafluoroborate as sources of electrophilic fluorine eliminated side reactions completely, albeit with lower yields of fluorinated product and longer reaction times. This result is in direct contrast to our previously reported copper-catalyzed system in which the use of other *N*-F reagents proved ineffective, yielding no fluorinated products.[103]

Having shown promise with simple alkanes, more complex substrates were next examined. Of importance: (1) sclareolide (entry **100**) demonstrated stereoselective α-fluorination at C2 and C3 of the A ring in a roughly 4:1 ratio respectively, a similar finding to Groves et al. using a Mn(porphyrin) catalyst, iodosobenzene as an oxidant and silver fluoride;[104] (2) aliphatic amides **102** and **103** were fluorinated under our reaction conditions; (3) competitive C–C bond fragmentation and/or secondary photochemical reactions of major fluorinated products, especially open-chained alkanes, **41** and **47**, was virtually

undetectable; (4) difluorination and rebound arylation from the photocatalyst is negligible.

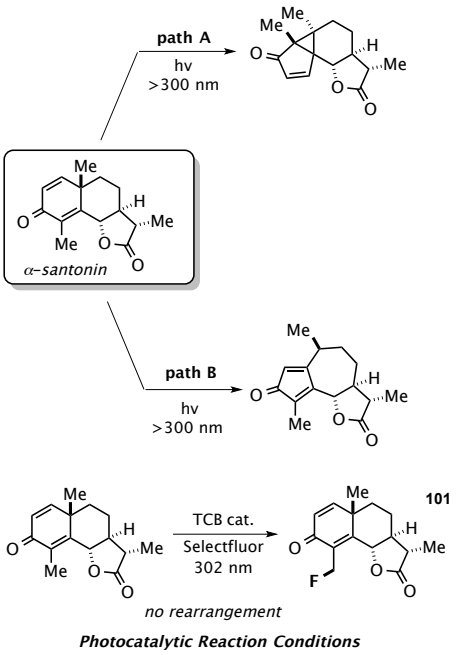
9.3) MECHANISTIC INSIGHT

Having demonstrated the reliability of our system for a host of simple to moderately complex alkanes, some initial mechanistic experiments were unertaken. In particular, the extent to which TCB was able to selectively absorb light in the presence of a competitor – namely a photoactive substrate and Selectfluor was of interest. To examine this question, the photoactive sesquiterpene lactone, α-santonin, was selected as a prototypical substrate, and mechanistic probe.

Under irradiative conditions, α-santonin undergoes a well-documented structural rearrangement initiated by cleavage of bond C4–C5 (path A) or C3–C4 (path B, Scheme 9.1);[202] as well, the resulting products should be suitable substrates for fluorination. The efficiency of the photocatalyst can be measured with respect to the extent of rearranged product in our reaction mixture. Upon analysis, fluorination of the α-methyl group was observed *exclusively*. Despite the classical propensity for rearrangement of dieneones, minimal to no structural reorganization of α-santonin was evident even after continued irradiation of the product allyl fluoride for an additional 16 h.

[202] (a) Chen, X.; Rinkevicius, Z.; Luo, Y.; Argen, H.; Cao, Z. *Chem. Phys. Chem*. **2012,** *13*, 353–362. (b) Zimmerman, H. E. *Pure Appl. Chem*. **2006,** *78*, 2193–2203. (c) Fisch, M. H. *Chem. Commun*. **1969,** 1472–1473.

Scheme 9.1. Photoinduced reaction of α-santonin



It may be postulated that the rearrangement of α-santonin in MeCN is slower than that for the rate of fluorination, such that the addition of fluorine prevents isomerization. Alternatively, selective sensitization of TCB or Selectfluor may inhibit sufficient irradiation of α-santonin required for rearrangement. In an attempt to answer this question, a series of control experiments were performed. In the absence of both photosensitizer and Selectfluor, rearrangement to the cyclopropyl ketone, lumisantonin (path A), occurs in high conversion. Conversely, in the absence of only the sensitizer, trace amounts of fluorinated product are observed along with a significant quantity of rearranged product. Finally, when α-santonin is irradiated at 302 nm with only sensitizer present, isomerization is again minimal, indicating that TCB inhibits isomerization. Based on the available

data, it is reasoned that preferential TCB sensitization followed by fluorination is the most likely pathway. Once fluorinated, rearrangement of the product does not occur to any significant extent.

As a final point of interest, the involvement of radicals in the reaction were examined by the use of a known radical clock the α,β-unsaturated aryl ester **80**. This compound has previously been shown to be a suitable probe for benzylic radical cyclizations.[203] Ideally, formation of the corresponding benzylic radical could lead to the standard fluorinated product **81** and/or the more diagnostic product **82** through a cyclization reaction.

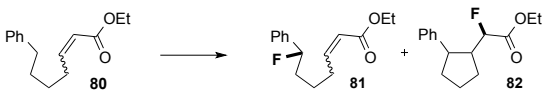


Figure 9.3. Radical clock analysis of α,β-unsaturated aryl ester

Experimentally, irradiation of 16, TCB, and Selectfluor over 16 h afforded a crude mixture of both products whose identity was determined by comparison to known literature values.[204] Additionally, the reaction was conducted in the presence of a known radical inhibitor, TEMPO. Although no trapped products could be isolated, the incorporation of TEMPO at any point during the reaction was found to inhibit the reaction, yielding little to no fluorinated products. The observed decrease in

[203] Bloom, S.; Sharber, S. A.; Holl, M. G.; Knippel, J. K.; Lectka, T. *J. Org. Chem*. **2013,** *78*, 11082–11086.
[204] For spectral data see: T. Morikawa, J. Uchida, Y. Hasegawa and T. Takeo, Chem. *Pharm. Bull.* **1991,** *39,* 2462–2464.

yield is also indicative of the participation of radicals, although further studies are needed to elucidate their exact role.

9.4) CONCLUDING REMARKS

Continued efforts to discern the precise mechanism of this new reaction will be made in addition to the search for new applications of our system to chemical synthesis, C–H activation and photocatalysis for the construction of complex fluorinated molecules.

CHAPTER 10

Photocatalyzed Benzylic Fluorination: Shedding "Light" on the Involvement of Electron Transfer

10.1) INTRODUCTION TO BENZYLIC FLUORINATION

As any conscientious student of organic chemistry knows, benzylic halogenations represent historically important chemical reactions.[205] Free radicals are often of paramount importance in benzylic halogenations and, as such, have been harnessed to give rise to chlorinations and brominations.[206] Benzylic fluorinations, especially using a hazardous reagent such as fluorine gas, are much more difficult;[207] therefore, straightforward and mild protocols for benzylic fluorination are desirable. An early example stems from the work of Sanford, who used chelating substrates in Pd(II) catalysis.[101] This discovery was followed by our work employing either a copper(I) based system[103] or $Fe(acac)_2$ as a catalyst,[114] followed by Groves's results with Mn-salen catalysts[104,113b] and Inoue's work on benzylic substitution through nitroxyl radical catalysis.[113c] All of

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[205] Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; Wiley-VCH: New York, **1999.**

[206] (a) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003,** *32*, 932-933. (b) Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc*. **1979,** *101*, 3060-3065. (c) Walling, C.; McGuinness, J. A. *J. Am. Chem. Soc*. **1969,** *91,* 2053-2058. (d) Pearson, R. E.; Martin, J. C. *J. Am. Chem. Soc*. **1963,** *85*, 354-355. (e) Walling, C.; Jacknow, B. B. *J. Am. Chem. Soc.* **1960,** *82*, 6108-6112.

[207] (a) Jaḥnisch,K.; Baerns,M.; Hessel,V.; Ehrfeld,W.; Haverkamp, V.; Löwe, H.; Wille, C.; Guber, A. *J. Fluorine Chem*. **2000,** *105*, 117-128. (b) Hutchinson, J.; Sandford, G. *In Organofluorine Chemistry*; Chambers, R. D., Ed.; *Topics in Current Chemistry*; Springer: Berlin, **1997**. (c) Schiemann, G.; Kühnhold, M.; Cernils, B. *Liebig Ann. Chem.***1968,** *714*, 62-75.

these protocols save one involve metal catalysis. Very recently, we reported a new method for aliphatic fluorination using the photocatalyst 1,2,4,5-tetracyanobenzene (TCB), Selectfluor, and MeCN as solvent.[208] This work was accompanied by a number of alternative sp^3 C-H fluorination methods by others using a host of photosensitizers including decatungstate ions, [209] anthraquinone,[210] and fluorenone.[211]

At least in some cases, it is widely held that photoexcited 1,2,4,5-tetracyanobenzene may operate by the abstraction of electrons from the substrate rather than hydrogen atom transfer (HAT), thereby forming discrete radical cations.[212] We envisioned such a system could prove complementary to catalysts believed to act through a HAT mechanism and useful for the fluorination of less reactive primary and secondary benzylic substrates (Figure 10.1).[213]

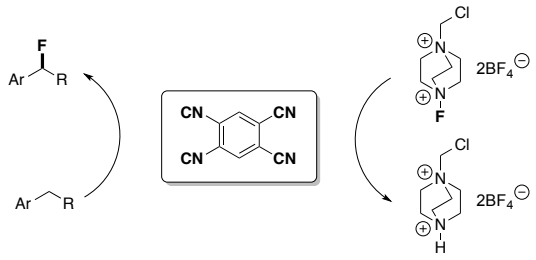


Figure 10.1. Photocatalysis for sp^3 benzylic fluorination

[208] Bloom, S.; Knippel, J. K.; Lectka, T. *Chem. Sci*. **2014,** *5*, 1175-1178.
[209] Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem., Int. Ed.* **2014,** *53*, 4690-4693.
[210] Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C.-H. *Chem. Commun*. **2014,** *50*, 8211-8214.
[211] Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc*. **2013,** *135*, 17494-17500.
[212] (a) Protti, S.; Fagnoni, M.; Monti, S.; RehÀault, J.; Poizat, O.; Albini, A. *RSC Adv*. **2012,** *2*, 1897-1904. (b) Schreiner, P. R.; Wittkopp, A.; Gunchenko, P. A.; Yaroshinsky, A. I.; Peleshanko, S. S.; Fokin, A. A. *Chemistry* **2001,** *7*, 2739-2744.
[213] (a) Chauhn, M. *IOSR J. Appl. Chem*. **2014,** *7*, 16-71. (b) Zavitsas, A. A. *Helv. Chim. Acta* **2006,** *89*, 2226-2242. (c) Singh, N.; O'Malley, P. J.; Popelier, P. L. *Phys. Chem., Chem. Phys*. **2005,** *7*, 614-619. (d) Gilliom, R. D.; Ward, B. F., Jr. *J. Am. Chem. Soc*. **1965,** *87*, 3944-3948.

10.2) PHOTOCATALYZED METHODOLOGY

We surveyed a number of benzylic compounds for reactivity using MeCN solvent, excess Selectfluor, and 10 mol % TCB, under photolysis with a pen lamp (λ_{max} = 302 nm). Examination of the products depicted in Table 10.1 highlights the selectivity for monofluorination at sterically accessible benzylic positions (methine or methylene) even in the presence of remote electron-withdrawing groups such as carbonyls, α,β- unsaturated ketones, or other functional groups that labilize adjacent protons. For simple alkylbenzenes, the relative reactivity of C_α-H bonds for methyl, ethyl, and isopropyl groups was determined. Interestingly, the rate of fluorination appears to decrease in the order 2° > 1° $\geq$ 3°, a result generally thought to be inconsistent with a free radical chain reaction (^{i}Pr > Et > Me).[214] Similarly, in the case of cymene, regioselective fluorination of the methyl group occurs despite the presence of a suitably reactive isopropyl substituent (**51**). Assuming formation of a radical cation, deprotonation of the methyl group is preferred due to the favorable π-C-H overlap that could be precluded in the isopropyl group for steric reasons.[215] Of further significance, we found that an unprotected benzylic aldehyde could be fluorinated without risk of acid fluoride formation (**106**), a common problem encountered with aldehydes in other benzylic fluorination protocols. Finally, electron-deficient aromatics demonstrated

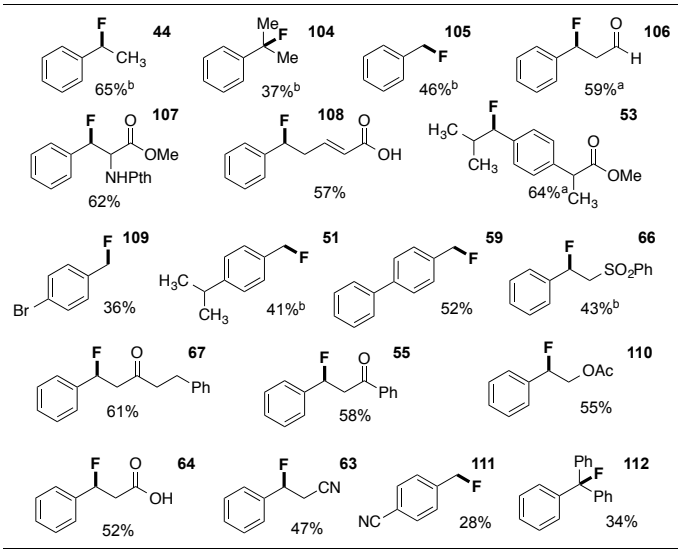
[214] Curran, D. P. *Synthesis* **1988,** *7*, 489-513.
[215] Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000,** *33*, 243-251.

some reactivity although these substrates have proven challenging to functionalize by alternative methods.

Considering the value of fluorinated amino acids to drug discovery and their potential utility in PET imaging, we next examined the fluorination of a phthalimide derived from *rac*-phenylalanine. Gratifyingly, fluorination proceeded smoothly to afford the fluorinated amino acid methyl ester **107** in 62% yield (1:1 diastereomeric mixture). It is also important to note that no decarboxylation was detected in carboxylic acid containing substrates, in contrast to precedent.[216] We also found that direct fluorination of the protected nonsteroidal anti-inflammatory (NSAID) ibuprofen methyl ester and pharmacophore dihydrochalcone could be achieved in 64% (compound **53**) and 58% (compound **55**) yields, respectively.

[216] (a) Koshima, H.; Ding, K.; Chisaka, Y.; Matsuura, T.; Ohashi, Y.; Mukasa, M. *J. Org. Chem.* **1996,** *61*, 2352-2357. (b) Koshima, H.; Ding, K. L.; Miyahara, I.; Hirotsu, K.; Kanzaki, M.; Matsuura, T. *J. Photochem. Photobiol. A: Chem*. **1995,** *87*, 219-223.

Table 10.1. Survey of benzylic fluorinated products



All reactions were performed under an inert atmoshere of N_2 and irradiated with a UV pen lamp (302 nm) for 24 h. (a) Isolated as the major fluorinated product with minor fluorinated isomers. (b) Yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard.

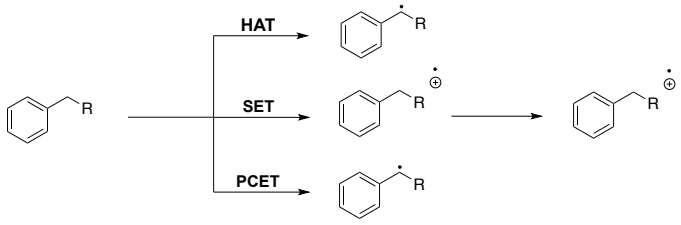
10.3) MECHANISTIC INSIGHT

At this point, we undertook some preliminary mechanistic experiments. Typically, photocatalyzed reactions proceed through one of a number of possible modes of action, including hydrogen atom transfer (HAT), electron transfer (ET), or a variety thereof termed proton-coupled electron transfer (PCET) (Scheme 10.1).[217] In the traditional HAT mechanism, homolytic hydrogen abstraction from a C-H bond results in formation of a nucleophilic carbon-centered radical that can react with various electrophiles. In an ET mechanism, either an oxidative or reductive activation is involved through formation of an electron donor-electron acceptor complex, permitting passage of electrons from one species of the

[217] (a) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc*. **2013,** *135*, 10022-10025. (b) Palmisano, G.; Augugliaro, V.; Pagliaro, M.; Palmisano, L. *Chem. Commun*. **2007,** 3425-3437.

exciplex to the other; the result is thus the formation of radical cations and anions.[218] In the case of PCET, transfer of an electron occurs with simultaneous loss of a proton to or from the substrate. This pathway is often encountered in biological and electrochemical systems displaying high redox activity and complexity.[219]

Scheme 10.1. Generation of radical intermediates during fluorination



To distinguish between these mechanisms, several parameters must be explored in more detail. Early work by Baciocchi[220] on the mechanism of side-chain oxidation of alkylbenzenes established that HAT and ET mechanisms exhibit distinctive selectivity patterns, thus representing a suitable probe for discerning between these two pathways. Baciocchi found that, in HAT mechanisms, the reactivity order ^{i}Pr > Et > Me is qualitatively observed. This finding may be explained by the fact that, in the HAT transition state, considerable breakage of the C-H bond occurs, and the C-H bond dissociation

[218] (a) Lewis, F. D. *In Photoinduced Electron Transfer*; Fox, M. A., Chanon, M., Eds.; Elsevier: Amsterdam, **1988**; Part C, Chapter 4.1. (b) Mariano, P. S.; Stavinoha, J. L. *In Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, **1984**; p 145.
[219] Weinberg, D. R.; Gagliard, C. J.; Hull, J. F.; Murphy, C. F.; Kent, C. A.; Westlake, B. C.; Paul, A.; Ess, D. H.; McCafferty, D. G.; Meyer, T. *J. Chem. Rev.* **2012,** *112*, 4016-4093.
[220] Baciocchi, E.; D'Acunzo, F.; Galli, C.; Lanzalunga, O. *J. Chem. Soc., Perkin Trans. 2* **1996,** 133-140.

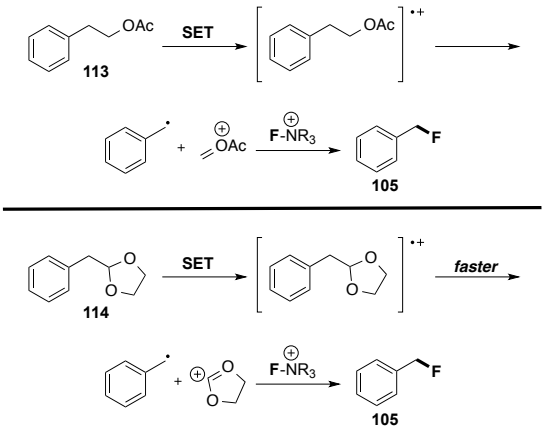
energy (BDE) increases in the progression 3° C-H < 2° C-H < 1° C-H. However, in the case of ET mechanisms, Baciocchi noted that the ^{i}Pr group is always less reactive than the Et group, and in a few cases even less reactive than the Me group. This finding is rationalized given that, in an ET mechanism, selectivity is determined in the radical cation deprotonation step, that, being irreversible, is also the step controlling the product distribution (in the manner of cymene). Moreover, cleavage of the C-H bond must be accompanied by an extensive electronic reorganization during which electrons from the benzylic C-H bond are transferred in part to the aromatic π-system, and it has been shown to possess a strong stereoelectronic component.[220] Analysis of the products in Table 10.1, namely compounds **44**, **104**, and **105**, suggests an ET mechanism for our reaction based on product yields alone; in fact, a competition experiment between these substrates revealed fluorination of ethylbenzene occurred exclusively. This finding is in direct contrast to our copper(I) catalyzed system, which has been recently shown to operate through a HAT mechanism.[221] In the copper system, competitive fluorination between toluene, ethylbenzene, and cumene is observed in a ratio of 1:6.4:3.8, the mild preference for ethylbenzene over cumene being attributed to a simple steric repulsion between proton abstractor and substrate. The difference in selectivities between these systems points to the possible influence of an alternative mechanism, most likely, an electron transfer process. This possibility is further augmented by an examination

[221] Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T. *J. Am. Chem. Soc.* **2014,** *136*, 9780-9791.

of the reactivity of a series of *p*-substituted toluene derivatives. Considering the rates of fluorination for *p*-bromotoluene, toluene, and *p*-cyanotoluene, *p*-cyanotoluene was found to react the slowest, while toluene reacted the fastest. This order correlates nicely with relative radical cation stabilities.

To probe the involvement of radical cations in our reaction, we envisaged the use of a compound that could render two distinct products depending on the initial intermediate formed, a benzylic radical or radical cation. We chose two candidates: 1-phenylethyl acetate **113** and 2-benzyl-1,3-dioxolane **114**, both of which are expected to form radical cation intermediates that can fragment into a benzyl radical and a stabilized cation (Scheme 9.2).

Scheme 10.2. Fragmentation of radical cations



For example, calculation of **113•+** at PBEPBE/cc-pVTZ shows a slightly elongated ArC-CO β-bond (1.525 Å) relative to the neutral and a considerably elongated ArC-H (1.136 Å) bond. In contrast, ArC-CO of **114•+** is 1.609 Å, and

the ArC-H bonds are fairly normal (1.090 Å). If radical cations are formed in the reaction, we thus predict that **114•+** should fragment more avidly than **113•+**. Hydrogen atom abstraction from **113** and **114** would lead to the substituted benzylic fluorides, whereas fragmentation should lead to fluorotoluene **105** (Scheme 10.2). Experimentally, photofluorination of **113** gave a mixture of **110** and **105** in an ~5:1 ratio (67% total yield). On the other hand, as predicted, **114** affords relatively more fluorotoluene (benzylic fluorinated **114** to **105** form in a 2:1 ratio 41% yield). Coincidentally, in an electron impact mass spectrometry experiment, **114** yields an approximately 2.5:1 mixture of parent ion and the dioxolanyl cation fragment, mirroring the results in solution.[222] For additional support, we turned to the reputedly obligatory outer sphere electron transfer agent potassium dodecatungstocobaltate ($K_5Co^{III}W_{12}O_{40}$).[223] Oxidation of **114** by an outer sphere electron transfer mechanism should provide **114•+** selectively. If radical cations are involved in the photofluorination reaction, we should expect to find a similar ratio of benzylic fluorinated **114** to **105** by substituting TCB for $K_5Co^{III}W_{12}O_{40}$ in the absence of light. As it turns out, reaction of **114** with $K_5Co^{III}W_{12}O_{40}$ and Selectfluor in MeCN solvent provided an ~2:1 ratio of benzylic fluorinated acetal to fluorotoluene, mimicking our earlier results with TCB. Thus, radical cations are almost assuredly involved in the reaction. We should also note that reaction of **114** using our copper(I) promoted fluorination conditions,[221] which

[222] Zhang, F.; Xu, D.-Q.; Luo, S.-P.; Liu, B.-Y.; Du, X.-H.; Zu, Z.-Y. *J. Chem. Res*. **2004,** 773-774.
[223] (a) Gupta, M.; Saha, S. K.; Banerjee, P. *Int. J. Chem. Kinet*. **1990,** *22*, 81-94. (b) Saha, S. K.; Bhattacharya, M.; Banerjee, A.; Banerjee, P. *Bull. Chem. Soc. Jpn*. **1989,** *62*, 3320-3327. (c) Gupta, M.; Saha, S. K.; Banerjee, P. *J. Chem. Soc., Perkin Trans. 2* **1988,** 1781-1785.

have been established to operate through HAT, gave no fragmented product. Instead, only benzylic fluorinated product was observed. Although a HAT mechanism would appear to be comfortably ruled out, discerning between ET and PCET pathways is often more difficult. Previously, it had been shown that TCB reacts with neat toluene under irradiative conditions through initial electron transfer followed by proton transfer to give substitution products.[224] Furthermore, formation of radical cation/anion pairs between irradiated TCB aromatic systems is well documented, seemingly favoring an ET pathway.[225]

10.4) CONCLUDING REMARKS

In conclusion, a photocatalyzed protocol for the mild, regioselective monofluorination of benzylic compounds has been reported. This system operates to afford a number of electronically and sterically diverse benzylic fluorides with potential medicinal and agrochemical value. Preliminary evidence for the involvement of radical cations in our reaction has helped to confirm these species as promising intermediates for halogenation reactions. Continued work will seek to elucidate the precise mechanism of this photofluorination system in tandem with the application of this method for the synthesis of complex fluorinated molecules.

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[224] (a) Yoshino, A.; Yamasaki, K.; Yonezawa, T.; Ohashi, M. *J. Chem. Soc., Perkin Trans. 1* **1975,** 735-737. (b) Yoshino, A.; Ohashi, M.; Yonezawa, T. *J. Chem. Soc. D: Chem. Commun*. **1971,** *97*.
[225] (a) Yamada, S.; Kimura, Y.; Ohashi, M. *J. Chem. Soc., Chem. Comm*. **1977,** 667-668. (b) Mataga, N.; Murata, Y. *J. Am. Chem. Soc*. **1969,** *91*, 3144-3152. (c) Shimada, M.; Masuhara, H.; Mataga, N. *Chem. Phys. Lett*. **1972,** *15*, 364-365.

CHAPTER 11

A Site-Selective Approach to β-Fluorination: Photocatalyzed Ring Opening of Cyclopropanols

11.1) INTRODUCTION TO β-FLUORINATION

Over the last two years, great strides have been made in the development of direct sp^3 C-H monofluorination methods. However, the methods we[103,114,203,208,221,226] and others[87,101,104,113,227] have reported are often limited to the derivatization of highly symmetric compounds, such as cycloalkanes, or those containing one activated site (e.g. benzylic). In substrates that contain many distinct carbon atoms, the problem of "scattershot" fluorination often arises, leading to undesirable mixtures of products. Expanding upon on these pioneering initial discoveries, the most logical next step is to focus on *directing* sp^3 C-F formation more effectively, which will allow new and desirable passageways to complex, selectively fluorinated molecules.

Conceptually, two potential routes for directing a radical fluorination event may involve (1) employing a directing group for C-H activation or (2) exploring selective C-C activation. In the former scenario, the use of directing groups for

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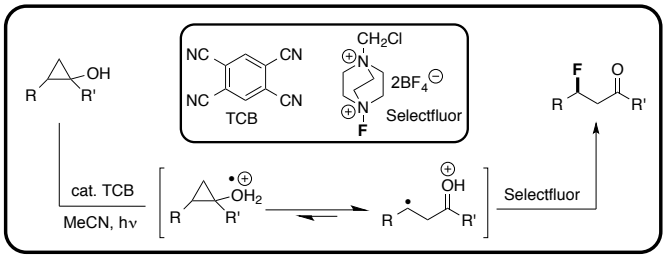
[226] Bloom, S.; McCann, M.; Lectka, T. *Org. Lett.* **2014**, *16*, 6338-6341.
[227] (a) Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494-17500. (b) Braun, M.-G.; Doyle, A. *J. Am. Chem. Soc.* **2013**, *135*, 12990-12993. (c) Xia, J.-B.; Zhu, C.; Chen, C. *Chem. Commun.* **2014**, *50*, 11701-11704. (d) Xia, J.-B.; Ma, Y.; Chen, C. *Org. Chem. Front.* **2014**, *1*, 468-472. (e) Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C.-H. *Chem. Commun.* **2014**, *50*, 8211-8214. (f) Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, O. C. *J. Org. Chem.*, **2014**, *79*, 8486-8490. (g) Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem. Int. Ed. Engl*. **2014**, *53*, 4690-4693.

sp^3 C-H fluorination has at least been ephemerally examined;[228] on the other hand, the use of C-C activation as a means to guide sp^3 fluorination is, to our knowledge, uncharted territory.[229] To examine this latter scenario, we envisioned that the homolytic cleavage of highly strained cyclopropanes may serve as an excellent mode for directing fluorination, as long as selective formation of the radical (or radical ion) that prompts C-C bond cleavage can be achieved. What is more, this chemistry should prove amendable to our previously reported photochemical fluorination methodology as *Cyclopropanol-based* starting materials are known to form radical cations under mild irradiation in the presence of photooxidants due to their high-lying HOMOs (Scheme 11.1).[230]

Scheme 11.1. Photocatalysis for the ring opening-β-fluorination of cyclopropanols



[228] Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134-7135.
[229] For recent reviews on C-C activation, see: (a) Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. *Angew. Chem. Int. Ed.* **2015,** *54*, 414-429. (b) Drahl, M. A.; Manpadi, M.; Williams, J. L. *Angew. Chem. Int. Ed.* **2013,** *52*, 11222-11251. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014,** *53*, 5504-5523.
[230] (a) Shubina, T. E.; Fokin, A. A. *WIREs Comput. Mol. Sci.* **2011**, *1*, 661-679. (b) Rinderhagen, H.; Mattay, J.; Nussbaum, R.; Bally, T. *Chem. Eur. J.* **2010**, *16*, 7121-7124. (c) Cooksy, A. L.; King, H. F.; Richardson, W. H. *J. Org. Chem.* **2003**, *68*, 9441-9462.

Consider the calculated structure of the representative radical cation shown in Figure 11.1-elongation (to 2.02 Å) of the weakest C-C bond between the C(Me)(OH) and C(H)(Me) fragments is observed. Thus, proton loss should selectively afford β-carbonyl radicals that can be subsequently fluorinated to afford β-fluorinated products.

Beyond proof-of-concept, note that the target β-fluorinated carbonyl-containing compounds are synthetically and medicinally useful. For example, the incorporation of a single fluorine atom at the β-position has been shown to influence the conformational integrity of cyclic amines and amides,[231] prevent mitochondrial β-oxidation of fatty acids,[232] and serve as an adequate positron emission tomography (PET) probe for elucidating a number of biosynthetic and metabolic pathways.[233] Yet, despite their broad utility, only a few methods exist to prepare β-fluorinated compounds.[234] It stands to reason that the development of a selective and efficient route to β-fluorides would be highly desirable, providing a much needed tool in the armamentarium of the medicinal chemist.

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[231] (a) Campbell, N. H.; Smith, D. L.; Reszka, A. P.; Neidle, S.; O'Hagan, D. *Org. Biomol. Chem*. **2011**, *9*, 1328-1331. (b) Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2009**, *11*, 943-946. (c) Venkatraman, S.; Lebsack, A. D.; Alves, K.; Gardner, M. F.; James, J.; Lingham, R. B.; Maniar, S.; Mumford, R. A.; Si, Q.; Stock, N.; Treonze, K. M.; Wang, B.; Zunic, J.; Munoz, B. *Biorg. Med. Chem. Lett*. **2009,** *19*, 5803-5806. (d) Black, L. A.; Nersesian, D. L.; Sharma, P.; Ku, Y.-Y.; Bennani, Y. L.; Marsh, K. C.; Miller, T. R.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. *Bioorg. Med. Chem*. **2007,** *17*, 1443-1446.

[232] (a) Bohm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*. **2004,** *5*, 637-643. (b) Tang, W.; Borel, A. G.; Fujimiya, T.; Abbott, F. S. *Chem. Res. Toxicol*. **1995**, *8*, 671-682.

[233] (a) Alauddin, M. M. *Am. J. Nucl. Med. Mol. Imaging* **2012,** *2*, 55-76. (b) Knust, E. J.; Kupfernagel, C.; Stockiln, G. J. *Nucl. Med*. **1979,** 20, 1170-1173.

[234] (a) Kim, K.-M.; Park, I.-H. *Synthesis*, **2004**, 2641-2644. (b) Marx, N. J. *Tetrahedron,* **1983**, *39*, 1529-1531. (c) Miller, R. D.; McKean, D. R. *Tetrahedron Lett*. **1980**, *21*, 2639-2642. (d) Johnson, C. R.; Cheer, C. J.; Goldsmith, D.J. *J. Org. Chem.* **1964**, *29*, 3320-3323.

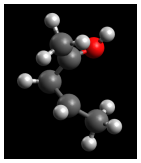
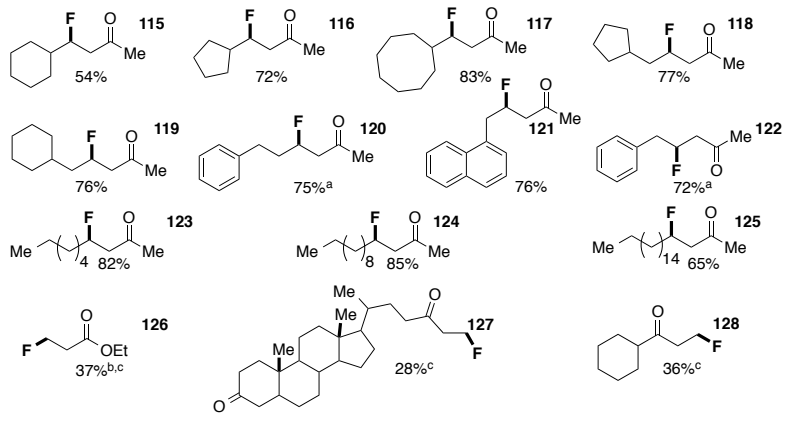


Figure 11.1. Calculated structure of *trans*-1,2-dimethylcyclopropanol radical cation (ωB97xD/cc-PVTZ, MeCN dielectric)

11.2) β-FLUORINATION METHODOLOGY

To begin our studies, we selected 2-cyclohexyl-1-methylcyclopropanol for screening purposes. Gratifyingly, UV irradiation (302 nm) with catalytic TCB (10 mol %) and Selectfluor (2.2 equiv.) at room temperature provided the desired β-fluoride **115** in 54% yield. Note that in the absence of TCB, no fluorinated products were observed. In addition, heating of 2-cyclohexyl-1-methylcyclopropanol and Selectfluor in MeCN provided a ~1:1 mixture of α- and β-fluorinated ketones and other fluorinated products; evidently, selective β-fluorination is only achievable under photocatalytic conditions. Moreover, other *N*-F reagents were also examined and found to give lower yields of fluorinated products. With these findings in mind, we decided to examine a variety of cyclopropanols derived from vinyl and allyl cycloalkanes, as well as aryl compounds. In each instance, β-fluorinated products were obtained in good to moderate yields and with excellent regioselectivity (Table 11.1).

Table 11.1. Survey of β-fluorinated products



All reactions were performed under an inert atmosphere of N_2 and irradiated with a UV pen lamp (302 nm) for 24 h. (a) Isolated as the major fluorinated product with minor fluorinated isomers. (b) Yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard. (c) Substrate for which xanthone was used as the photocatalyst.

Remarkably, the reaction is highly selective toward C-C bond cleavage/fluorination over direct sp^3 C-H fluorination, despite the previous application of this system to aliphatic fluorination.[226d] Compounds **115-119** contain multiple potential fluorination sites on the cyclopentane, cyclohexane, and cyclooctane rings, but only trace ring fluorination products are observed in the crude ^{19}F NMR, avoiding the aforementioned issue of scattershot fluorination.

Additionally, the selective formation of β-fluorinated compounds **120-122** reflects the propensity of cyclopropanols to direct the fluorination event. Benzylic substrates offer a much tougher test, but even in the presence of a more activated benzylic site, C-C bond cleavage *is still favored,* providing β-fluorinated products in upwards of 72% yield, although trace amounts of putative benzylic products are observed in some cases.

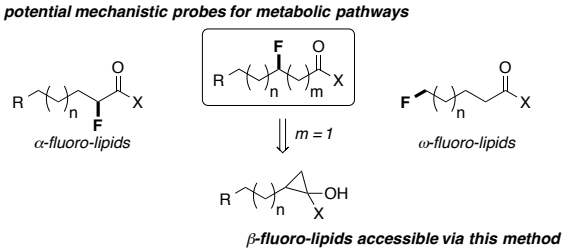


Figure 11.2. β-fluoro-lipids accessible as potential biological probes

In order to probe the selectivity of the reaction in situations where indiscriminate fluorination could be especially problematic, we turned our attention to cyclopropanols possessing linear aliphatic side chains. These compounds could conceivably serve as precursors to β-fluorinated fatty acids, whose proteo-counterparts are frequently metabolized by oxidative cleavage of a β-C-H bond (Figure 11.2).[235] The selective inclusion of a single fluorine atom at the β-position could therefore prove particularly useful in deterring this pathway.[236] Furthermore, monofluorinated lipids have found considerable use as probes for studying the interaction between drugs or peptides and lipid membranes.[237] Toward this effort, we found that 10-, 14-, and 20-carbon β-fluorinated ketones **123**-**125** could be prepared from the respective cyclopropanols. Polyfluorination and direct aliphatic fluorination were not

[235] (a) Zhang, L.; Keung, W.; Samokvalov, V.; Wang, W.; Lopaschuk, G. D. *Biochimica et Biophysica Acta*, **2010**, *1801*, 1-22. (b) Freneaux, E.; Fromenty, B.; Berson, A.; Labbe, G.; Degott, C.; Letteron, P.; Larrey, D.; Pessayre, D. *J. Pharm. Exp. Ther.* **1990**, *2*, 529-535. (c) Stoffel, W.; Caesar, A. *Hoppe-Seyler's Z. Physiol. Chem*. **1965**, *341*, 76-83.

[236] (a) Ojima, L. *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**. (b) Liu, P.; Sharon, A.; Chu, C. K. *J. Fluorine. Chem*. **2008**, *129*, 743-766. (c) Böhm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Khun, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*. **2004**, *5*, 637-643.

[237] (a) Krafft, M. P. *Adv. Drug. Deliv. Rev*. **2001**, *47*, 209-228. (b) Hirsh, D. J.; Lazaro, N.; Wright, L. R.; Boggs, J. M.; Mclntosh, T. J.; Schaefer, J.; Blazyk, J. *Biophysical J*. **1998**, *4*, 1858-1868. (c) Post, J. F. M.; De Ruiter, E. E. J.; Brendsen, H. J. C. *FEBS Lett.* **1981**, *132*, 257-260.

competitive with β-fluorination, as compounds **123-125** were isolated in 65-85% yield.

As another point of interest, we investigated the scope of the reaction for the synthesis of primary β-fluorides. Terminal alkyl fluorides have been shown to be effective reagents for inexpensive nickel or copper-catalyzed cross coupling reactions,[238] although these methods have remained underdeveloped due to their preparative difficulty. We found that a host of primary fluorides are prepared in modest yields. For instance, compound **126** was formed in 37% yield from 1-ethoxy-cyclopropanol, also notably expanding the scope of this reaction to β-fluoroesters. In another example, ring opening/fluorination of a non-natural steroid, a methyl lithocholate derivative,[239] was found to yield the primary fluoride **127** in 28% yield. As expected, yields for primary β-fluorides were often lower than secondary β-fluorides, a possible result of the diminished stability of primary radicals as compared to secondary. In an effort to improve upon these results, we found that replacement of TCB by xanthone as the active photocatalyst provided moderate increases in yields for primary fluorides.

At this point, we considered alternative applications for this method. We explored the use of a tertiary cyclopropanol that could undergo oxidative ring-opening/fluorination to afford a ring-expanded β-fluoride. For a representative example, we selected cyclopropanol **129**, as tandem ring expansion/fluorination should lead to β-fluorocycloheptanone **130**. Cycloheptanone cores are present in

[238] (a) Terao, J.; Watabe, H.; Kambe, N. *J. Am. Chem. Soc*. **2005**, *11*, 3656-3657. (b) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc*. **2003**, *19*, 5646-564.
[239] Enhsen, A.; Kramer, W.; Wess, G. *Drug. Disc. Today*, **1998**, *9*, 409-418.

pharmaceuticals such as bencyclane, a spasmolytic agent and vasodilator, as well as a vital constituent in many fragrances and polymers (Figure 11.3).[240] In this instance, photochemical fluorination proceeded smoothly to afford β-fluorocycloheptanone **130** in 62% yield. Note that minimal byproducts resulting from elimination or dimerization were observed in the crude reaction mixture, despite the likely participation of reactive radical intermediates.

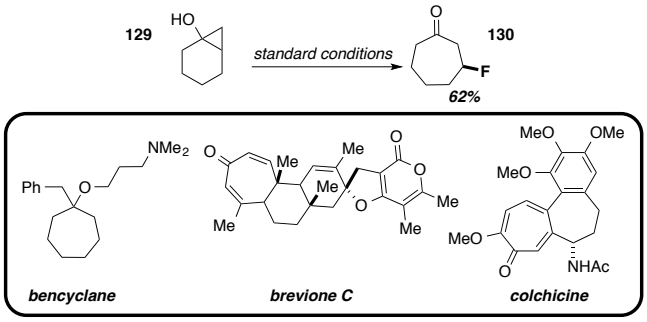


Figure 11.3. Tandem ring expansion/β-fluorination to access cycloheptanone core

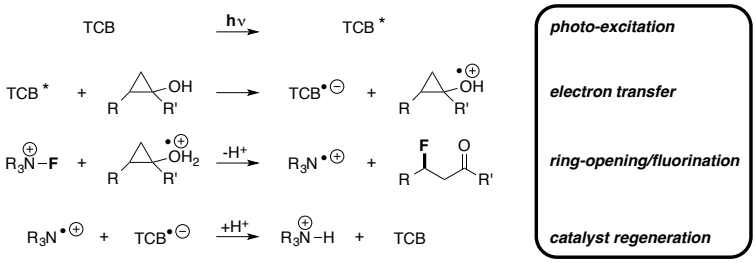
11.3) MECHANISTIC INSIGHT

Finally, a general mechanistic proposal for the reaction is shown in Scheme 11.2. Photoexcitation of TCB is known to yield a powerful oxidant that, in this

[240] (a) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *23*, 8854-857. (b) Bieroń, K.; Kostk-Trabka, E.; Starzyk, D.; Goszcz, A.; Grodziǹska, L.; Korbut, R. *Acta Anglo*. **2005**, *3*, 157-172. (c) Cornils, B.; Lappe, P. *Ullmann's Encyclopedia of Industrial Chemistry.* Wiley-VCH, Weinheim, **2005**. (d) Schmalz, H.-G.; Graening, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 3230-3256. (e) Kishore, G.; Kishore, K. *Polymer*, **1995**, *9*, 1903-1910.

instance, putatively abstracts an electron from the substrate.[241] The resultant cyclopropanol radical cation prompts C-C bond elongation while relieving ring strain (Figure 11.1); this is accompanied by proton loss to selectively afford a β-carbonyl radical. As precedented, Selectfluor can then act as an atomic source of fluorine to directly fluorinate the radical.[1e][5] Lastly, the Selectfluor radical cation retrieves the electron from the TCB radical anion, as well as the excess proton from the reaction medium, thus generating an ammonium salt byproduct and regenerating the TCB catalyst.

Scheme 11.2. Proposed mechanism for photocatalyzed site-selective β-fluorination



[241] (a) Christl, M.; Braun, M.; Deeg, O. *Org. Biomol. Chem.*, **2013**, *11*, 2811–2817. (b) Protti, S.; Fagnoni, M.; Monti, S.; Rehault, J.; Poizat, O.; Albini, A. *RSC Adv*. **2012**, *2*, 1897–1904. (c) Fokin, A. A.; Gunchenko, P. A.; Peleshanko, S. A.; von Ragué Schleyer, P.; Schreiner, P. R. *Eur. J. Org. Chem*. **1999**, 855–860. (d) Mella, M.; Fagnoni, M.; Freccero, M.; Fasani, E.; Albini, A. *Chem. Soc. Rev*. **1998**, *27*, 81–89. (e) Mella, M.; Freccero, M.; Albini, A. *Tetrahedron,* **1996**, *52*, 5549–5562. (f) Mella, M.; Freccero, M.; Albini, A. *J. Chem. Soc., Chem. Commun*. **1995**, *1*, 41–42.

11.4) CONCLUDING REMARKS

In conclusion, a photocatalyzed protocol for the selective ring-opening/β-fluorination of cyclopropanols is reported. This system is synthetically mild, operationally simple, and can be employed to afford a number of electronically and sterically diverse β-fluorination carbonyl-containing compounds. Furthermore, various fluorinated products with high medicinal and agrochemical values can be prepared by employing this method. Continued work will seek to elucidate the precise mechanism of the photochemical fluorination system along with the application of this method to the synthesis of complex fluorinated molecules.

CHAPTER 12

EXPERIMENTAL METHODS

12.1) EXPERIMENTAL DETAILS FOR CHAPTER 2

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and acid chlorides were dried and distilled by standard methods. ^{1}H spectra were acquired on a BRUKER 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a BRUKER 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and or $CFCl_3$ (δ 0.00 ppm). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d= doublet, t = triplet, q = quartet), integration, coupling constants [Hz]). IR data was obtained using a NEXUS 670 FT-IR with a NaCl cell. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 2-difluoro-*N*-2-diphenylacetamide (**2**),[242] 2-difluoro-*N*-phenyl-2-(phenylthio)acetamide (**6**),[243] ethyl 2,2-difluoro-2-phenylacetate (**11**),[244] 2,2-difluoro-2-phenylethanol (**12**),[245] methyl 2,2-difluoro-2-

[242] Guidotti, J.; Metz, F.; Tordeux, M.; Wakselman, C. *Synlett* **2004**, *10*, 1759-1762.
[243] Suryanarayanan, V.; Chellammal, S.; Noel, M. *J. Fluorine Chem.* **1999**, *93*, 53-60.
[244] Lheureux, A.; Beaulieu, F.; Laflamme, F.; Couturier, M.; Bennett, C.; Clayton, S.; Tovell, D.; Bill, D. R.; Mirmehrabi, M.; Tadayon, S. *J. Org. Chem.* **2010**, *75*, 3401-3411.
[245] Schlosser, M.; Bruegger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron* **2004**, *60*, 7731-7742.

phenylacetate (**13**), [246] 2,2-difluoro-2-phenylacetic acid (**14**), [247] benzyl 2,2-difluoro-2-phenylacetate (**15**), [248] *N*,*N*-diethyl- 2,2-difluoro-2-phenylacetamide (**16**)[249] were consistent with the literature precedents.

General Procedure for the Syntheses of Fluorinated Products:

An oven-dried, 10 mL round bottom flask equipped with a stir bar was placed under an atmosphere of N_2. KBARF (7.2 mg, 0.01 mmol, 0.1 equiv) and Selectfluor (177 mg, 0.5 mmol, 5 equiv) were added followed by MeCN (0.9 mL) and the mixture allowed to stir for 10 min. Under a stream on N_2, $Sn(OTf)_2$ (8.4 mg, 0.02 mmol, 0.2 equiv) was added neat to the mixture followed by pyridine (0.08 mL, 79.0 mg, 10.0 equiv). Then, 0.3 mL of a 0.34 M solution of phenylacetyl chloride (0.1 mmol, 1.0 equiv) in MeCN was added dropwise via syringe pump. Once the addition was complete, the reaction was allowed to stir at room temperature for 3 h. The reaction was cooled to 0°C and aniline (0.032 mL, 0.35 mmol, 3.5 equiv) was added and the reaction was allowed to warm to room temperature overnight. The product was extracted into CH_2Cl_2 and washed with water. The organics were dried with $MgSO_4$ and filtered through celite. The solvents were removed by rotary evaporation and the residue subjected to

[246] Parisi, M. F.; Gattuso, G.; Notti, A.; Raymo, F. M.; Abeles, R. H. *J. Org. Chem.* **1995**, *60*, 5174-5179.
[247] Ilayaraja, N.; Manievel, A.; Velayutham, D.; Noel, M. *J. Fluorine Chem.* **2008**, *129*, 185-192.
[248] Bravo, P.; Pregnolato, M.; Resnati, G. *J. Org. Chem.* **1992**, *57*, 2726-2731.
[249] Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2003**, *68*, 6063-6065.

column chromatography on silica gel with a mixture of ethyl acetate/hexanes as eluent.

Characterization:

2-(4-bromophenyl)-2,2-difluoro-N-phenylacetamide (3). White solid. mp = 95°C; ^{1}H NMR ($CDCl_3$): δ 8.01 (br s, 1H), 7.56-7.49 (m, 5H), 7.32-7.28 (m, 2H), 7.15-7.11 (m, 2H) ; ^{13}C NMR ($CDCl_3$): δ 161.3 (t, *J* = 66 Hz), 135.8 (s), 132.3 (s), 131.8 (s), 131.5 (t, *J* = 55 Hz), 129.2 (s), 127.4 (t, *J* = 12 Hz), 125.8 (s), 120.1 (s), 114.4 (t, *J* = 480 Hz); ^{19}F NMR ($CDCl_3$): δ -102.5 (s, 2F); IR (CH_2Cl_2): 1710 cm^{-1}; HRMS-(ESI$^+$) calcd for $C_{14}H_{10}BrF_2NONa^+$: 347.9804, found 347.9813.

2-(4-chlorophenyl)-2,2-difluoro-N-phenylacetamide (4). White solid. mp = 94°C; ^{1}H NMR ($CDCl_3$): δ 8.06 (br s, 1H), 7.53 (d, 2H, *J* = 8 Hz), 7.48 (d, 2H, 8 Hz), 7.35 (d, 2H, *J* = 8 Hz), 7.30 (t, 2H, *J* = 8 Hz), 7.11 (t, 1H, *J* = 15 Hz); ^{13}C NMR ($CDCl_3$): δ 160.4 (t, *J* = 62 Hz), 136.4 (t, *J* = 4 Hz), 134.8 (s), 130.0 (t, *J* = 51 Hz), 128.2 (s), 127.9 (s), 126.2 (t, *J* = 12 Hz), 124.8 (s), 119.1 (s), 113.3 (t, *J* = 507 Hz); ^{19}F NMR ($CDCl_3$) δ -102.5 (s, 2F); IR (CH_2Cl_2): 1691 cm^{-1}; HRMS-(ESI)+calcd for $C_{14}H_{10}ClF_2NONa^+$: 304.0309 found 304.0319 .

2-(4-fluorophenyl)-2,2-difluoro-N-phenylacetamide (5). White solid. mp = 93°C; ^{1}H NMR ($CDCl_3$): δ 8.01 (br s, 1H), 7.63-7.59 (m, 2H), 7.50 (d, 2H, *J* = 8 Hz), 7.30 (t, 2H, *J* = 16 Hz), 7.16-7.07 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 162.1 (s),

160.8 (t, J = 55 Hz), 134.9 (s), 128.2 (s), 127.1 (m), 124. 7 (s), 119.2 (s), 114.9 (s), 114.7 (s), 113.4 (t, J = 501 Hz); ^{19}F NMR ($CDCl_3$): δ -101.7 (s, 2F), -109.4 (m, 1F); IR (CH_2Cl_2): 1711 cm^{-1}; HRMS-$(ESI)^+$ calcd for $C_{14}H_{10}F_3NONa^+$: 288.0604, found 288.0611.

ethyl 2,2-difluoro-3-oxo-3-(phenylamino)propanoate (7). Colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.95 (br s 1H), 7.51 (d, 2H, J = 10 Hz), 7.34-7.30 (m, 3H), 7.27-7.23 (m, 1H), 4.34 (q, 2H, J = 21 Hz, 7 Hz), 1.31 (t, 3H, J = 14 Hz); ^{13}C NMR ($CDCl_3$): δ 165.7.0 (s), 163.8 (s), 138.6 (s), 129.3 (s), 129.0 (m), 125.9 (t, J = 150 Hz), 64.2 (s), 13.8 (s); α-carbon could not be resolved; ^{19}F NMR ($CDCl_3$): δ -112.3 (s, 2F); IR (CH_2Cl_2): 1737 cm^{-1}; HRMS-$(ESI)^+$ calcd for $C_{11}H_{11}F_2NO_3Na^+$: 266.0597, found 266.0586.

2,2-difluoro-N-phenyl-2-(thiophen-2-yl)acetamide (8). Colorless oil. ^{1}H NMR ($CDCl_3$): δ 8.03 (br s, 1H), 7.52 (d, 2H, J = 8 Hz), 7.43-7.40 (m, 2H), 7.31-7.27 (m, 2H), 7.14-7.10 (m, 1H), 7.00-6.99 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 159.9 (t, J = 60 Hz), 134.9 (s), 132.6 (t, J = 60 Hz), 128.3 (s), 128.2 (s), 127.8 (t, J = 12 Hz), 126.0 (s), 124.7 (s), 119.2 (s), 112.0 (t, J = 503 Hz); ^{19}F NMR ($CDCl_3$): δ -91.7 (s, 2F); IR (CH_2Cl_2): 1711 cm^{-1}; HRMS-$(ESI)^+$ calcd for $C_{12}H_9F_2NOSNa^+$: 276.0263, found 276.0271.

2-(3,5-difluorophenyl)-2,2-difluoro-N-phenylacetamide (9). White solid. mp =

94°C ; ^{1}H NMR ($CDCl_3$): δ 8.00 (br s, 1H), 7.50 (d, 2H, *J* = 8 Hz), 7.31 (t, 2H, *J* = 16 Hz), 7.17-7.12 (m, 3H), 6.89 (m, 1H); ^{13}C NMR (CDCl3): δ 163.1 (d, *J* = 12 Hz), 160.6 (d, *J* = 12 Hz), 159.7 (t, *J* = 61 Hz), 134.7 (s), 128.3 (s), 124.9 (s), 119.2 (s), 112.4 (t, *J* = 504 Hz), 108.4 (m), 105.7 (t, *J* = 50 Hz); ^{19}F NMR (CDCl3): δ -103.0 (s, 2F), -107.5 (m, 2F); IR (CH_2Cl_2): 1691 cm^{-1}; HRMS-$(ESI)^+$ calcd for $C_{14}H_9F_4NONa^+$: 306.0510, found 306.0522.

2,2-difluoro-N-phenyl-2-(3-(trifluoromethyl)phenyl)acetamide (10). Colorless oil. ^{1}H NMR (CDCl3): δ 8.06 (br s, 1H), 7.88 (s, 1H), 7.83 (d, 1H, *J* = 8 Hz), 7.71 (d, 1H, *J* = 8 Hz), 7.57-7.50 (m, 3H), 7.30 (t, 2H, *J* = 16 Hz), 7.14 (t, 1H, *J* = 16 Hz); ^{13}C NMR ($CDCl_3$): δ 160.0 (t, *J* = 60 Hz), 135.3 (s), 134.7 (s), 132.5 (t, *J* = 51 Hz), 131.4 (s), 130.3 (d, *J* = 35 Hz), 128.3 (s), 126.9 (s), 124.9 (s), 123.8 (s), 121.4 (d, *J* = 55 Hz), 119.2 (s), 113.0 (t, *J* = 501 Hz); ^{19}F NMR ($CDCl_3$): δ - 102.9 (s, 2F), -63.2 (m, 3 F); IR (CH_2Cl_2): 1711 cm^{-1}; HRMS-$(ESI)^+$ calcd for $C_{15}H_{10}F_5NONa^+$: 338.0572, found 338.0565.

12.2) EXPERIMENTAL DETAILS FOR CHAPTER 3

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and acid chloride compounds were dried and distilled by standard methods. All reactions were performed on a 0.24 mmol scale with respect to the acid chloride except for β-naphthylacetyl chloride (1 g scale). ^{1}H spectra were acquired on a 400 MHz NMR spectrometer in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR spectrometer in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and or trichlorofluoromethane ($CFCl_3$, δ 0.00 ppm). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants [Hz], integration). IR data was obtained using FT-IR with a NaCl cell. High-resolution mass spectra (HRMS) were recorded using ESI-TOF (electrospray ionization–time-of-flight) mass spectrometry. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 2,2-difluoro-N-phenyl-2-(thiophene-2-yl)acetamide **(8)** was consistent with literature precedent.[62] Compound **25** was reported as crude spectra due to product decomposition. Spectral data was processed with ACD/NMR Processor Academic Edition.[267]

General Procedure for Synthesis of α,α-Difluorinated Products:

An oven-dried, 100 mL, round-bottom flask equipped with a stir bar was placed under an atmosphere of N_2. Selectfluor (8.66, 24.4 mmol, 5.00 equiv), 1,8-naphthyridine (0.064 g, 0.49 mmol, 0.10 equiv), potassium tetrakis(pentafluorophenyl)borate (0.175 g, 0.244 mmol, 0.0500 equiv), tin(II) trifluoromethanesulfonate (0.248 g, 0.488 mmol, 0.100 equiv), and β-naphthylacetyl chloride (1.00 g, 4.88 mmol, 1.00 equiv) were added. Pyridine (3.9 mL, 48 mmol, 10. equiv) was then added dropwise. The mixture stirred for 3 h, at which time the reaction was quenched with aniline (4.0 mL, 44 mmol, 9.0 equiv). The product was extracted into CH_2Cl_2 and washed with 1 M HCl followed by saturated $NaHCO_3$ solution. The organics were dried with $MgSO_4$ and filtered through Celite. The solvents were removed by rotary evaporation, and the residue was subjected to column chromatography on silica with a mixture of ethyl acetate/hexanes as eluent to afford 2,2-difluoro-2-(naphthalen-2-yl)-*N*-phenylacetamide as a white solid (0.72 g, 49%).

Computational Methods:

The Gaussian 09260 package and Spartan '10 were used for all calculations. Geometry optimizations of 1,8-naphthyridine, pyridine, acylpyridine, and acylnaphthyridine were determined at the B3LYP/6-311++G** level. Geometry optimization of the chelated enolate was determined at the B3LYP/ 6-31G* (LANL2DZ on Sn) level.

Characterization:

2,2-Difluoro-2-(naphthalen-2- yl)-N-phenylacetamide (17). brown solid; mp 128–129 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 8.13 (br s, 1H), 7.96–7.87 (m, 3H), 7.73 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.58 (m, 4H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 162.2 (t, *J* = 30.7 Hz), 136.1 (s), 134.3 (s), 132.4 (s), 131.0 (s), 129.8 (t, *J* = 24.8 Hz), 129.2 (s), 129.1 (s), 128.9 (s), 128.8 (s), 127.8 (s), 127.7 (s), 127.0 (s), 126.0 (t, *J* = 7 Hz), 122.8 (s), 122.1 (t, *J* = 5.1), 120.2 (s), 115.1 (t, *J* = 253 Hz); ^{19}F NMR ($CDCl_3$) δ −102.3 (s, 2F); IR (C=O) 1714 cm^{-1} ; HRMS (ESI^+) calcd for $C_{18}H_{13}F_2NONa^+$ 320.0863, found 320.0865; yield 0.72 g (49%) and 37.8 mg (52%).

2,2-Difluoro-2-(naphthalen-1-yl)-N-phenylacetamide (18). amorphous solid; ^{1}H NMR ($CDCl_3$) δ 8.26 (dt, *J* = 7.2, 1.0 Hz, 1H), 8.24 (br s, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.91 (t, *J* = 8 Hz, 2H), 7.61–7.50 (m, 5H), 7.35 (t, *J* = 8 Hz, 2H), 7.19 (tt, *J* = 7.4, 1.6 Hz, 1H); 13C NMR (CDCl3) δ 161.8 (t, *J* = 30.7 Hz), 136.1 (s), 134.1 (s), 132.3 (s), 129.6 (s), 129.2 (s), 128.9 (s), 128.1 (t, *J* = 23.4 Hz), 127.4 (s), 126.4 (s), 125.6 (s), 125.4 (t, *J* = 9.1 Hz), 124.5 (t, *J* = 3.3 Hz), 124.4 (s), 120.2 (s), 116.2 (t, *J* = 254 Hz); ^{19}F NMR ($CDCl_3$) δ −98.4 (s, 2F); IR (C=O) 1717 cm^{-1} ; HRMS (ESI^+) calcd for $C_{18}H_{13}F_2NONa^+$ 320.0863, found 320.0861; yield 57.8 mg (80%).

2-([1,1′-Biphenyl]-4-yl)-2,2-difluoro-N-phenylacetamide (19). white solid; mp 154–156 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (br s, 1H), 7.77–7.67 (m, 4H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.41–7.35 (m, 2H), 7.96–7.87 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 161.8 (t, *J* = 31.5 Hz), 148.3 (s), 144.1 (s), 140.0 (s), 136.1 (s), 131.4 (t, *J* = 25.6 Hz), 129.3 (s), 128.9 (s), 128.0 (s), 127.4 (d, *J* = 17.6 Hz), 126.1 (t, *J* = 6.2 Hz), 125.6 (s), 120.2 (s), 112.4 (t, *J* = 255 Hz); ^{19}F NMR ($CDCl_3$) δ –102.6 (s, 2F); IR (C=O) 1715 cm^{-1} ; HRMS (ESI^+) calcd for $C_{20}H_{15}F_2NONa^+$ 346.1019, found 346.1021; yield 43.2 mg (55%).

2,2-Difluoro-N-phenyl-2-(p-tolyl)acetamide (20). tan solid; mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (br s, 1H), 7.57–7.54 (m, 4H), 7.33 (t, *J* = 8 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.0 (t, *J* = 31.5 Hz), 140.3 (s), 129.0 (s), 128.7 (s), 128.3 (s), 128.1 (s), 125.5 (t, *J* = 2.9 Hz), 125.4 (s), 120.2 (s), 114.0 (t, *J* = 254 Hz), 20.3 (s); ^{19}F NMR ($CDCl_3$) δ –102.4 (s, 2F); IR (C=O) 1715 cm^{-1} ; HRMS (ESI^+) calcd for $C_{15}H_{13}F_2NONa^+$ 284.0863, found 284.0867; yield 38.5 mg (60%).

2,2-Difluoro-2-(4-methoxyphenyl)-N-phenylacetamide (21). yellow solid; mp 83–84 °C; ^{1}H NMR ($CDCl_3$) δ 8.14 (br s, 1H), 7.60–7.54 (m, 4H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.6 (s), 136.1 (s), 131.6 (s), 129.1 (s), 127.2 (t, *J* = 6.2 Hz), 125.5 (s), 124.6 (t, *J* = 25.6 Hz), 120.1 (s), 114.9 (t, *J* = 254 Hz), 114.0 (s), 55.4 (s); ^{19}F

NMR ($CDCl_3$) δ −100.2 (s, 2F). IR (C=O) 1715 cm^{-1} ; HRMS (ESI^+) calcd for $C_{15}H_{13}F_2NO_2Na^+$ 300.0812, found 300.0815; yield 46.1 mg (68%).

2-(Benzo[d][1,3]dioxol-5-yl)-2,2-difluoro-N-phenylacetamide (22). tan solid; mp 117–118 °C; ^1H NMR ($CDCl_3$) δ 8.09 (br s, 1H), 7.59–7.56 (m, 2H), 7.35 (t, *J* = 8 Hz, 2H), 7.21–7.13 (m, 3H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.01 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 161.8 (t, *J* = 31.5 Hz), 149.9 (s), 148.0 (s), 136.1 (s), 129.2 (s), 126.5 (s), 126.3 (s), 125.6 (s), 120.2 (s), 120.1 (t, *J* = 6.6 Hz), 114.7 (t, *J* = 255 Hz), 108.3 (s), 106.3 (t, *J* = 6.2); ^{19}F NMR ($CDCl_3$) δ −101.1 (s, 2F); IR (C=O) 1716 cm^{-1} ; HRMS (ESI^+) calcd for $C_{15}H_{11}F_2NO_3Na^+$ 314.0605, found 314.0601; yield 51.5 mg (72%).

2-(2-Chlorophenyl)-2,2-difluoro-N-phenylacetamide (23). blue solid; mp 105–107 °C; ^1H NMR ($CDCl_3$) δ 8.26 (br s, 1H), 7.79– 7.86 (m, 1H), 7.57–7.55 (m, 2H), 7.34–7.49 (m, 5H), 7.16–7.24 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 161.0 (t, *J* = 29.2 Hz), 136.1 (s), 132.3 (t, *J* = 1.4 Hz), 131.8 (s), 130.8 (s), 130.6 (s), 129.2 (s), 128.3 (t, *J* = 8.7 Hz), 126.9 (s), 125.6 (s), 120.2 (s), 114.1 (t, *J* = 255 Hz); ^{19}F NMR ($CDCl_3$) δ −102.3 (s, 2F); IR (C=O) 1716 cm^{-1} ; HRMS (ESI^+) calcd for $C_{14}H_{10}ClF_2NONa^+$ 304.0317, found 304.0320; yield 34.2 mg (50%).

2,2-Difluoro-2-(4-nitrophenyl)-N-phenylacetamide (24). brown solid; mp 101–102 °C; ^1H NMR ($CDCl_3$) δ 8.32 (d, *J* = 9 Hz, 2H), 8.21 (br s, 1H), 7.90 (d, *J*

= 8.8 Hz, 2H), 7.59–7.55 (m, 2H), 7.41–7.34 (m, 2H), 7.22 (tt, *J* = 7.5, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 160.6 (s), 149.6 (s), 138.4 (t, *J* = 25.8 Hz), 135.6 (s), 129.3 (s), 127.2 (t, *J* = 6 Hz), 126.0 (s), 123.7 (s), 120.2 (s), 113.8 (t, *J* = 256 Hz); ^{19}F NMR ($CDCl_3$) δ –103.4 (s, 2F); IR (C=O) 1717 cm^{-1} ; HRMS (ESI^+) calcd for $C_{14}H_{10}F_2N_2O_3Na^+$ 315.0557, found 315.0552; yield 36.4 mg (51%).

2,2-Difluoro-N-phenyl-2-(thiophene-2-yl)acetamide (8). Spectral and analytical data were in agreement with previous reports. Yield: 38.9 mg (63%).

2-(4-(1,3-Dioxoisoindolin-2-yl)phenyl)-2,2-difluoro-N-phenylacetamide (25). ^1H NMR ($CDCl_3$) δ 7.95 (m, 2H) 7.80 (m, 2H) 7.55– 7.32 (m, 6H) 7.06 (br. s. 1H); ^{13}C NMR ($CDCl_3$) δ 165.9 (s), 165.2 (s), 161.6 (s), 133.6 (s), 130.5 (s), 130.0 (s), 128.1 (t, *J* = 6.2 Hz), 126.3 (s), 126.2 (s), 125.6 (s), 122.8 (t, *J* = 8.7 Hz), 121.8 (s), 120.0 (s), 119.3 (s), 115.5 (t, *J* = 255 Hz); ^{19}F NMR ($CDCl_3$) δ –105.96 (s, 2F). IR (C=O) 1716, 1727 cm^{-1} ; HRMS (ESI^+) calcd for $C_{22}H_{14}F_2N_2O_3Na^+$ 415.0870, found 415.0877; yield 43.8 mg (46%).

2,2-Difluoro-2-(7-methyl-2-oxo-2H-chromen-4-yl)-N-phenylacetamide (26). brown solid; mp 172–173 °C; ^1H NMR ($CDCl_3$) δ 8.19 (br s, 1H), 7.72 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 9.2 Hz, 2H), 7.39 (m, 2H), 7.25–7.11 (m, 3H), 6.78 (s, 1H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.6 (s), 159.4 (s), 154.2 (s), 144.8 (t, *J* = 24 Hz), 144.2 (s), 135.5 (s), 129.3 (s), 126.1 (s), 126.1 (s), 125.6 (s), 120.3 (s),

117.6 (s), 115.1 (t, J = 10.3 Hz), 113.1 (t, J = 257 Hz), 112.3 (s), 21.6 (s); ^{19}F NMR ($CDCl_3$) δ –103.55 (s, 2F); IR (C=O) 1718, 1731 cm^{-1} ; HRMS (ESI^+) calcd for $C_{18}H_{13}F_2NO_3Na^+$ 352.0761, found 352.0758; yield 32.1 mg (40%).

2-(5,6-Dimethyl-9-oxo-9H-xanthen-4-yl)-2,2-difluoro-N-phenylacetamide (27). tan solid; mp 217–219 °C; ^{1}H NMR ($CDCl_3$) δ 8.49 (d, J = 7.9 Hz, 1H), 8.43 (br s, 1H), 8.10 (d, J = 6.6 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.3 Hz, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.39 (t, J = 7.9 Hz, 2H), 7.24–7.16 (m, 2H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.4 (s), 160.8 (s), 154.0 (s), 153.1 (s), 144.9 (s), 136.1 (s), 132.6 (t, J = 8.1 Hz), 130.2 (s), 129.3 (s), 126.5 (s), 125.7 (s), 125.0 (s), 123.5 (s), 123.2 (s), 122.1 (s), 121.2 (t, J = 24.9 Hz), 119.9 (s), 119.7 (s), 114.4 (t, J = 256 Hz), 20.7 (s), 11.6 (s); ^{19}F NMR ($CDCl_3$) δ –101.68 (s, 2F); IR (C=O) 1660, 1720 cm^{-1} ; HRMS (ESI^+) calcd for $C_{23}H_{17}F_2NO_3Na^+$ 416.1074, found 416.1070; yield 19.2 mg (20%).

Ethyl (2,2-difluoro-2-(naphthalen-1-yl)acetyl)phenylalaninate (28). amorphous solid; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 7.4 Hz, 1H), 7.98 (d, J = 8.2, 1H), 7.89 (m, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.55 (m, 2H), 7.48 (t, J = 7.7 Hz, 1H), 7.18 (m, 3H), 6.93 (d, J = 7.4 Hz, 2H), 6.87 (d, J = 7.4 Hz, 1H), 4.91 (dd, J = 12.9, 5.87 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.15 (qd, J = 12.1, 5.8 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4 (s), 163.4 (t, J = 30.7 Hz), 134.9 (s), 133.9 (s), 132.0 (s), 129.4 (s), 129.1 (s), 128.7 (s), 128.5 (s), 128.4 (s), 128.2 (s), 127.9 (s), 127.3 (s), 127.2 (s), 126.3 (s), 125.3 (t, J = 8.8 Hz), 124.6 (t, J = 3.3

Hz), 124.4 (s), 115.9 (t, J = 253 Hz), 61.8 (s), 53.2 (s), 37.4 (s), 14.0 (s); ^{19}F NMR ($CDCl_3$) δ −101.68 (s, 2F); IR (C=O) 1720, 1740 cm^{-1} ; HRMS (ESI^+) calcd for $C_{23}H_{21}F_2NO_3Na^+$ 420.1387, found 420.1381; yield 81.3 mg (84%).

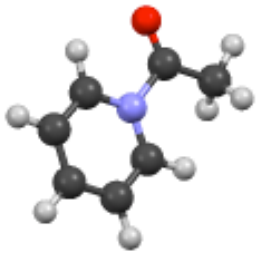
(S)-N-(4-(3-Ethyl-2,6-dioxopiperidin-3-yl)phenyl)-2,2-difluoro-2- (naphthalen-1-yl)acetamide (29). white solid; mp 210–212 °C; ^{1}H NMR (C_2D_6OS) δ 11.05 (s, 1H), 10.94 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.70 (m, 3H), 7.35 (d, J = 8.8 Hz, 2H), 2.38 (d, J = 3.1 Hz, 2H), 2.19 (m, 2H), 1.88 (sxt, J = 7.2 Hz, 2H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (C_2D_6OS) δ 175.6 (s), 172.7 (s), 161.8 (t, J = 31.5 Hz), 136.3 (s), 136.1 (s), 133.5 (s), 132.1 (s), 129.1 (s), 128.8 (s), 128.1 (s), 127.9 (s), 127.6 (s), 126.8 (s), 126.5 (s), 125.7 (t, J = 8.4 Hz), 124.8 (s), 123.9 (s), 121.1 (s), 116.1 (t, J = 252 Hz), 54.9 (s), 49.9 (s), 32.1 (s), 29.1 (s), 25.9 (s), 8.9 (s); ^{19}F NMR (C_2D_6OS) δ −96.22 (2F); IR (C=O) broad 1710 cm^{-1} ; HRMS (ESI^+) calcd for $C_{25}H_{22}F_2N_2O_3Na^+$ 459.1496, found 459.1491; yield 78.9 mg (74%)

N-((3s,5s,7s)-Adamantan-1-yl)-2,2-difluoro-2-(naphthalen-1-yl)- acetamide (30). white solid; mp 136–138 °C; ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.55 (m, 3H), 6.19 (br s, 1H), 2.06 (s, 9H), 1.69 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 161.7 (t, J = 29.3 Hz), 133.0 (s), 130.9 (s), 128.7 (s), 128.1 (s), 127.8 (s), 126.1 (s), 125.2

(s), 124.3 (t, J = 9.1 Hz), 123.6 (s), 123.4 (s), 114.9 (t, J = 253 Hz), 51.9 (s), 46.7 (s), 40.1 (s), 35.1 (s), 28.3 (s); ^{19}F NMR ($CDCl_3$) δ –99.29 (dd, J = 451.6, 267.0 Hz, 2F); IR (C=O) 1705 cm^{-1} ; HRMS (ESI^+) calcd for $C_{22}H_{23}F_2NONa^+$ 378.1645, found 378.1649; yield 67.8 mg (80%).

(5S,8R,9S,10S,13S,14S)-10,13-Dimethyl-17-oxohexadecahydro- 1H-cyclopenta[a]phenanthren-3-yl 2,2-Difluoro-2-(naphthalen-1- yl)acetate (31). white solid; mp 179–180 °C; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.9 (m, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.59–7.49 (m, 3H), 4.82 (spt, J = 5.3 Hz, 1H), 2.42 (dd, J = 19.2, 8.3 Hz, 1H), 2.05 (m, 1H), 1.90 (m, 1H), 1.79– 1.72 (m, 4H), 1.68–1.42 (m, 4H), 1.30–1.14 (m, 6H), 0.86 (m, 2H), 0.83 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.8 (s), 162.9 (t, J = 34.4 Hz), 132.8 (s), 128.8 (s), 128.5 (s), 128.2 (s), 128.0 (s), 127.7 (s), 126.1 (s), 125.2 (s), 123.8 (t, J = 9.5 Hz), 123.4 (s), 123.2 (s), 113.3 (t, J = 251 Hz), 53.1 (s), 50.2 (s), 46.6 (s), 43.5 (s), 35.4 (s), 34.8 (s), 34.5 (s), 33.9 (s), 32.3 (s), 30.4 (s), 29.6 (s), 27.0 (s), 25.9 (s), 20.7 (s), 19.4 (s), 12.7 (s), 11.2 (s); ^{19}F NMR ($CDCl_3$) δ –100.47 (s, 2F); IR (C=O) 1735, 1756 cm^{-1} ; HRMS (ESI^+) calcd for $C_{31}H_{36}F_2O_3Na^+$ 517.2530, found 517.2537; yield 50.3 mg (42%).

Acyl Pyridine



SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-311++G**
Number of shells: 94
Number of basis functions: 254
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
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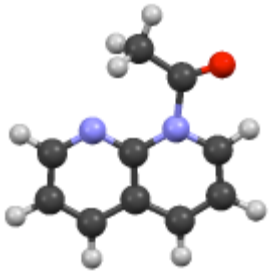
2	-401.4015372	0.008402	0.028658
3	-401.4020804	0.003656	0.012766
4	-401.4021856	0.001139	0.003240
5	-401.4021957	0.000617	0.002694
6	-401.4021984	0.000098	0.000451

Acyl naphthyridine

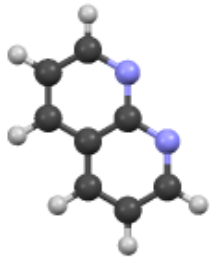


SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3
Job type: Reading previous wavefunction
Program Wall Time: 0:01:43.0
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-311++G**
Number of shells: 123
Number of basis functions: 349
SCF model:

A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-571.1218898	0.026687	0.127275
2	-571.1139464	0.056993	0.160596
3	-571.1118790	0.043438	0.127290
4	-571.1152007	0.063914	0.121107
5	-571.1173585	0.040548	0.154239
6	-571.1174501	0.048978	0.167773
7	-571.1159446	0.046017	0.137321
8	-571.1156235	0.041520	0.142244
9	-571.1182594	0.043872	0.123582
10	-571.1195774	0.034803	0.109485
11	-571.1193406	0.040878	0.159332
12	-571.1159352	0.037554	0.137704
13	-571.1179932	0.037640	0.127465
14	-571.1163104	0.045528	0.153135
15	-571.1175983	0.035723	0.114653
16	-571.1172826	0.032827	0.126958
17	-571.1173800	0.028489	0.113692
18	-571.1188846	0.033501	0.136040
19	-571.1200098	0.024799	0.108856
20	-571.1170009	0.028922	0.120453
21	-571.1212102	0.018048	0.112961
22	-571.1191474	0.027907	0.120189
23	-571.1223488	0.019356	0.095078
24	-571.1179763	0.028446	0.088185
25	-571.1243509	0.010815	0.112012
26	-571.1157264	0.030318	0.100130
27	-571.1246245	0.010266	0.131685
28	-571.1201839	0.024836	0.082638
29	-571.1252698	0.002850	0.038118
30	-571.1249947	0.007064	0.027975
31	-571.1253159	0.001115	0.005791
32	-571.1252933	0.001675	0.005674
33	-571.1253224	0.000397	0.004479
34	-571.1253183	0.000669	0.002966
35	-571.1253265	0.000240	0.002238
36	-571.1253241	0.000583	0.001639
37	-571.1253245	0.000116	0.001649

1,8-naphthyridine



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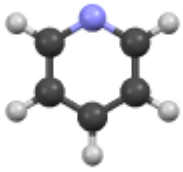
3	7	0	1.154917	-1.423803	-0.000092
4	6	0	1.248325	1.393596	0.000031
5	6	0	0.000002	-0.705629	-0.000040
6	6	0	2.399723	0.649527	0.000062
7	6	0	0.000000	0.725970	-0.000005
8	7	0	-1.154917	-1.423805	0.000112
9	1	0	3.377349	1.116341	0.000201
10	1	0	-1.276090	2.478766	-0.000146
11	1	0	1.276092	2.478767	0.000167
12	6	0	-2.291253	-0.763546	0.000094
13	1	0	-3.196354	-1.366970	-0.000019
14	6	0	-2.399724	0.649529	-0.000063
15	1	0	-3.377353	1.116338	-0.000203
16	6	0	-1.248327	1.393594	-0.000024

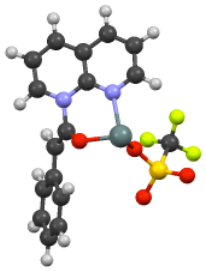
Pyridine



opt b3lyp/6-311++g(d,p) maxdisk=3GB geom=connectivity

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.000000	0.000000	1.416604
2	6	0	0.000000	0.000000	-1.383044
3	6	0	0.000000	1.141771	0.721225
4	6	0	0.000000	-1.141771	0.721225
5	6	0	0.000000	-1.196725	-0.671625
6	6	0	0.000000	1.196725	-0.671625
7	1	0	0.000000	2.056782	1.307240
8	1	0	0.000000	-2.056782	1.307240
9	1	0	0.000000	-2.153718	-1.180132
10	1	0	0.000000	2.153718	-1.180132
11	1	0	0.000000	0.000000	-2.467371

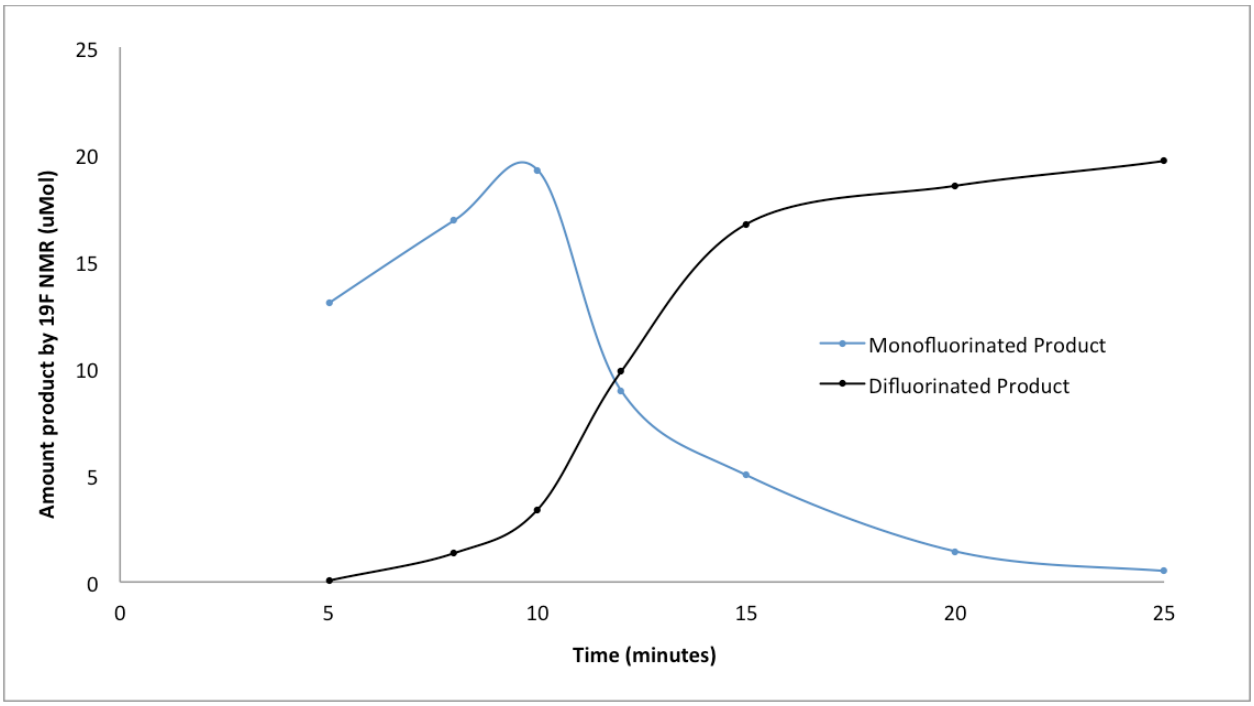
Proposed chelated intermediate



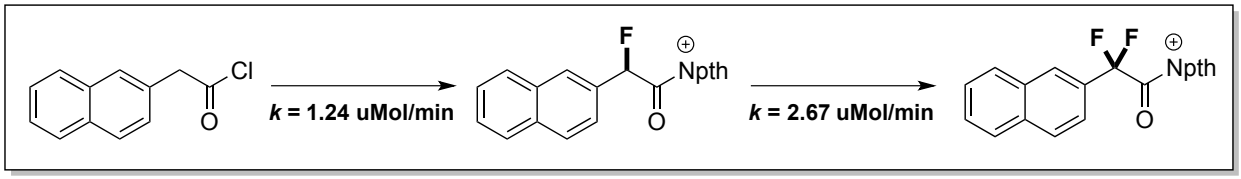
opt b3lyp/lanl2dz scrf=(solvent=acetonitrile) maxdisk=24GB geom=connectivity

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-4.704408	2.497544	-0.340375
2	6	0	-4.167817	1.557673	-0.316295
3	1	0	-5.663114	0.395214	-1.350817
4	6	0	-4.686979	0.399766	-0.876445
5	7	0	-2.174531	0.358875	0.410690
6	6	0	-3.924718	-0.805361	-0.837843
7	6	0	-2.917078	1.488461	0.336432
8	6	0	-2.636909	-0.775047	-0.212505
9	6	0	-4.403119	-2.014435	-1.420419
10	1	0	-2.520359	2.366139	0.835803
11	6	0	-3.611177	-3.154311	-1.378896
12	1	0	-5.383742	-2.030905	-1.884797
13	1	0	-3.944718	-4.100745	-1.784196
14	6	0	-2.334892	-3.079850	-0.798428
15	1	0	-1.688990	-3.945283	-0.740835
16	7	0	-1.835461	-1.924059	-0.274626
17	6	0	-0.419199	-1.923837	0.168051
18	6	0	0.503272	-2.452447	-0.683756
19	1	0	0.151033	-2.753593	-1.667286
20	6	0	1.937472	-2.642792	-0.442684
21	6	0	4.725692	-3.097178	-0.124925
22	6	0	2.566430	-2.437018	0.815416
23	6	0	2.735179	-3.086542	-1.532355
24	6	0	4.112854	-3.308442	-1.377519
25	6	0	3.944586	-2.664533	0.966948
26	1	0	1.972456	-2.112735	1.661548
27	1	0	2.268817	-3.255611	-2.500887
28	1	0	4.705069	-3.645094	-2.224444
29	1	0	4.411441	-2.505641	1.935870
30	1	0	5.791816	-3.269109	-0.001470
31	8	0	-0.225179	-1.407690	1.395943
32	50	0	-0.460432	0.494465	2.022266
33	8	0	2.006789	3.509792	1.017758
34	16	0	1.908016	2.255185	-0.003242
35	8	0	0.669961	1.186800	0.379523
36	8	0	3.264709	1.482398	-0.426842
37	6	0	1.088681	2.967047	-1.702377
38	9	0	-0.208078	3.368352	-1.454049
39	9	0	1.090595	1.976648	-2.661478
40	9	0	1.824605	4.045285	-2.148635

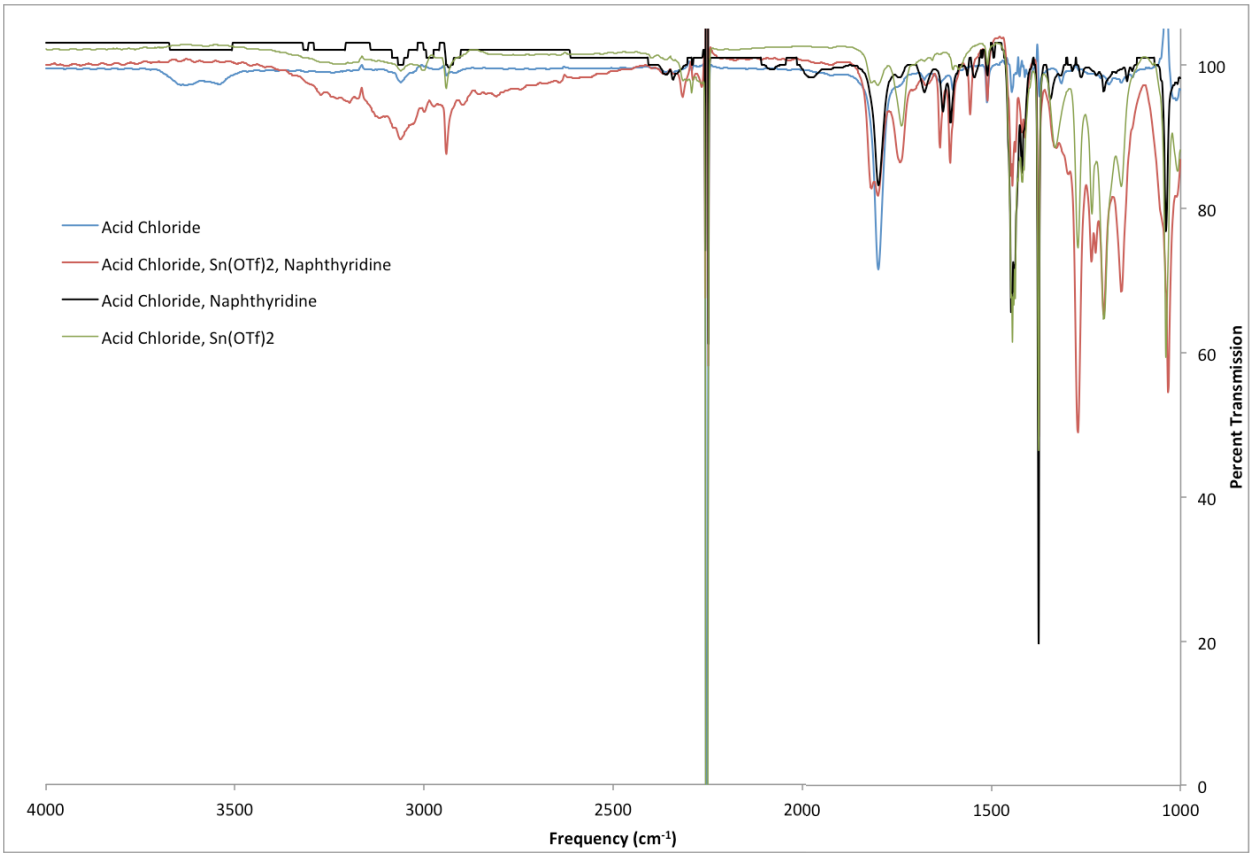
^{19}F NMR Kinetic Data

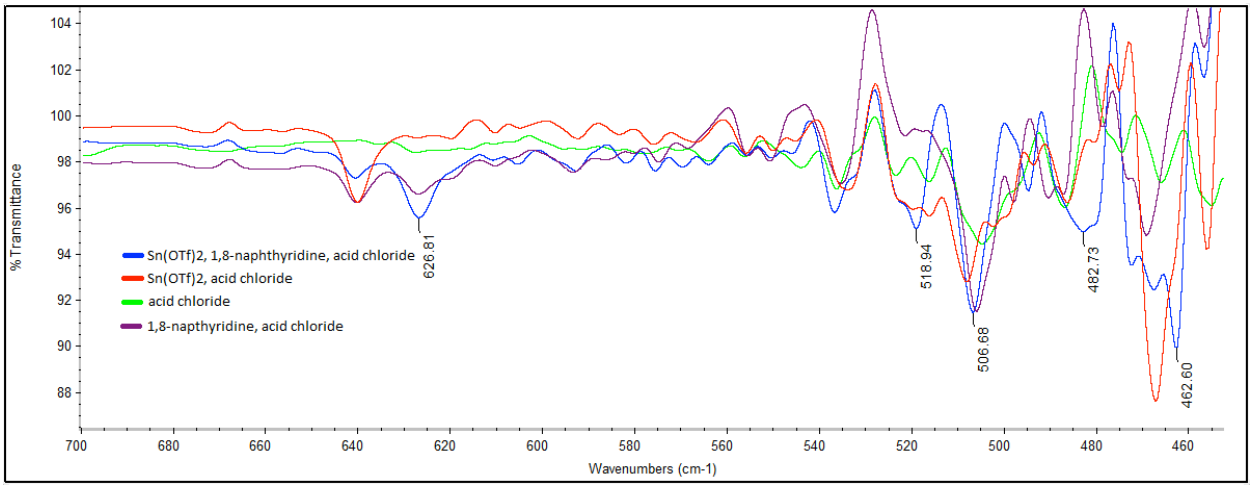


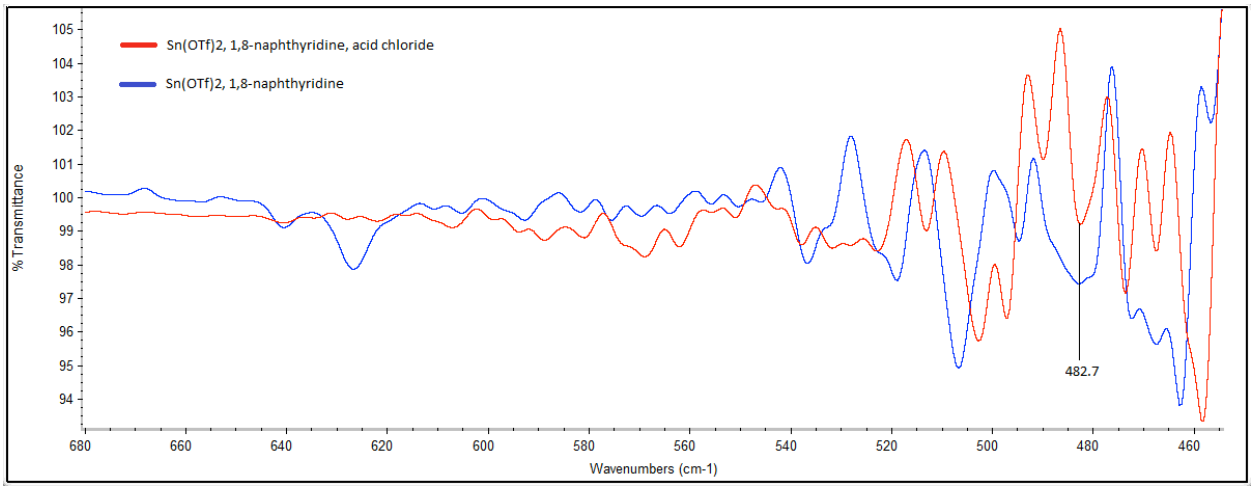
Initial rates calculated:
First fluorination – 1.24 uMol/min
Second fluorination – 2.67 uMol/min



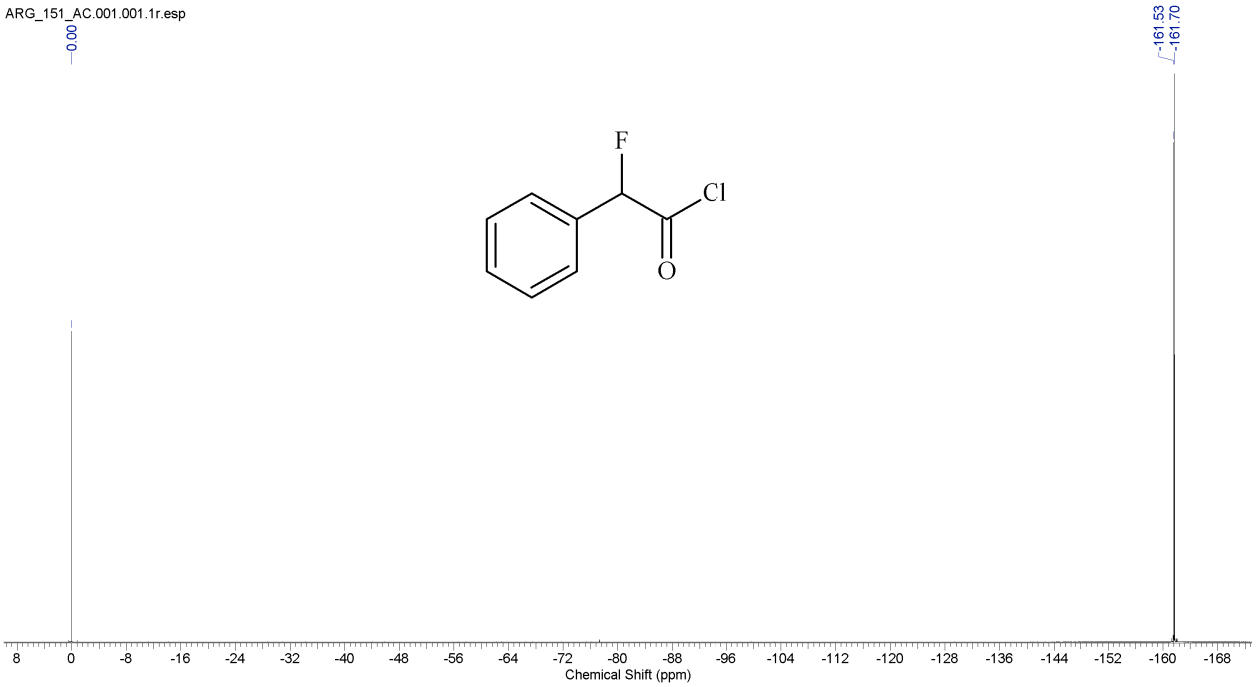
Infrared Spectroscopy Data

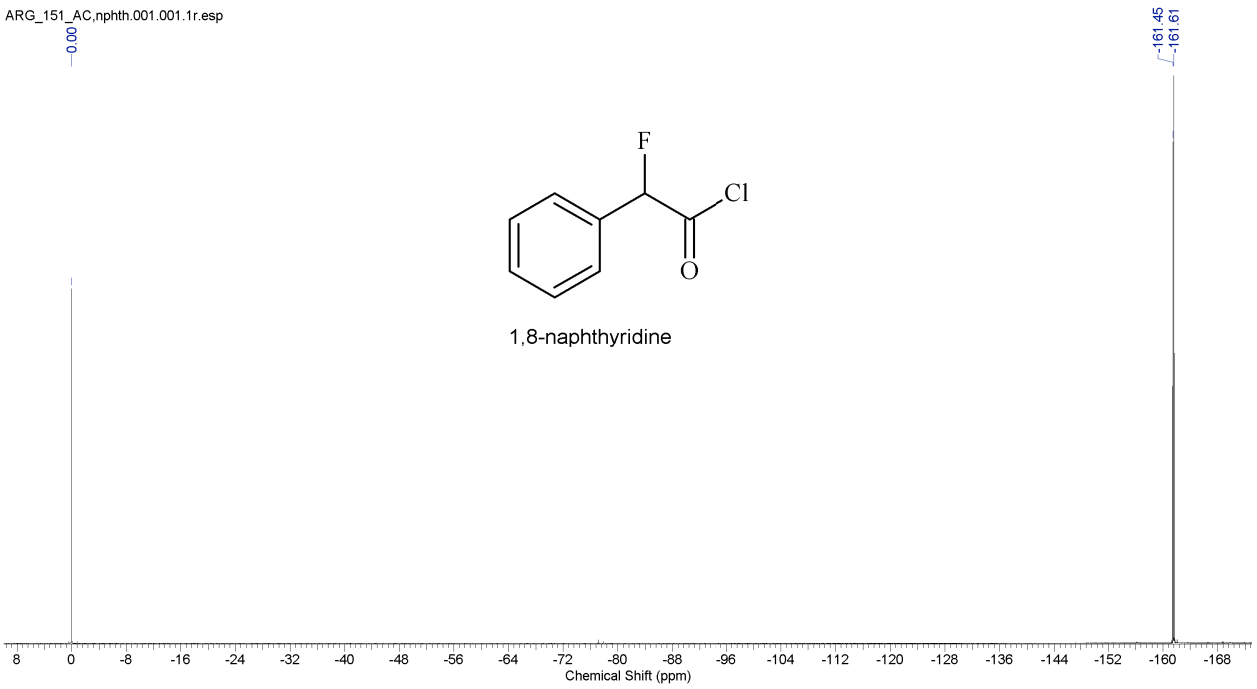


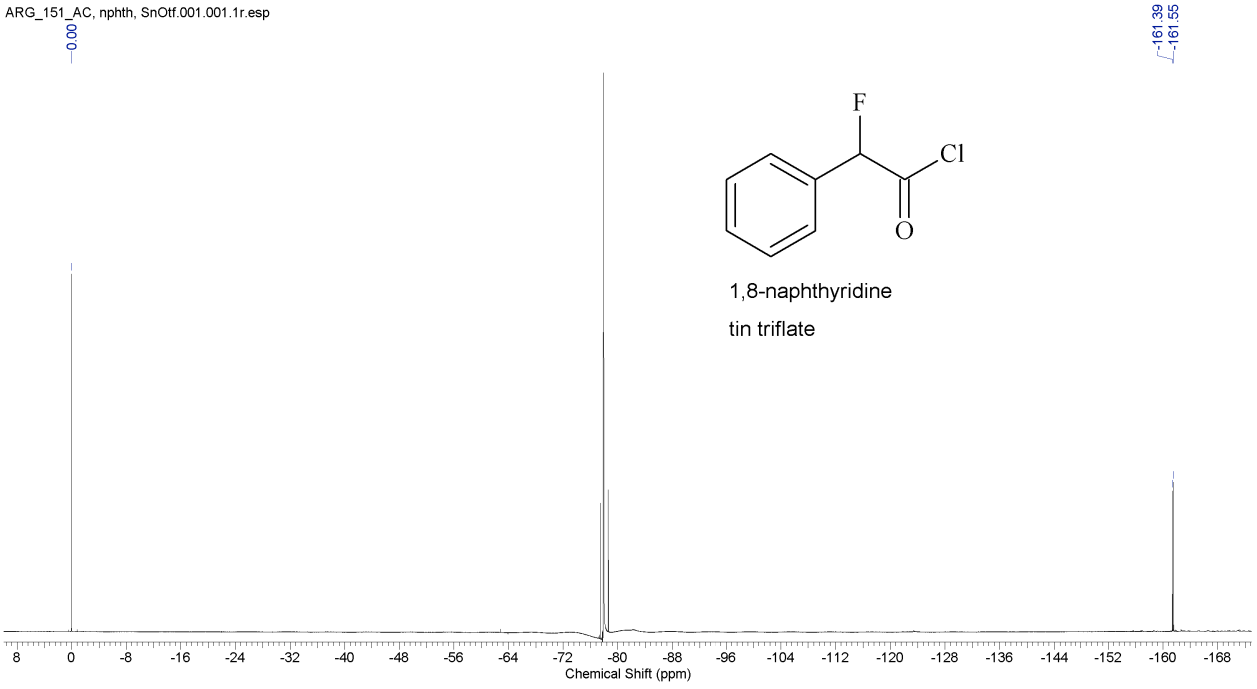


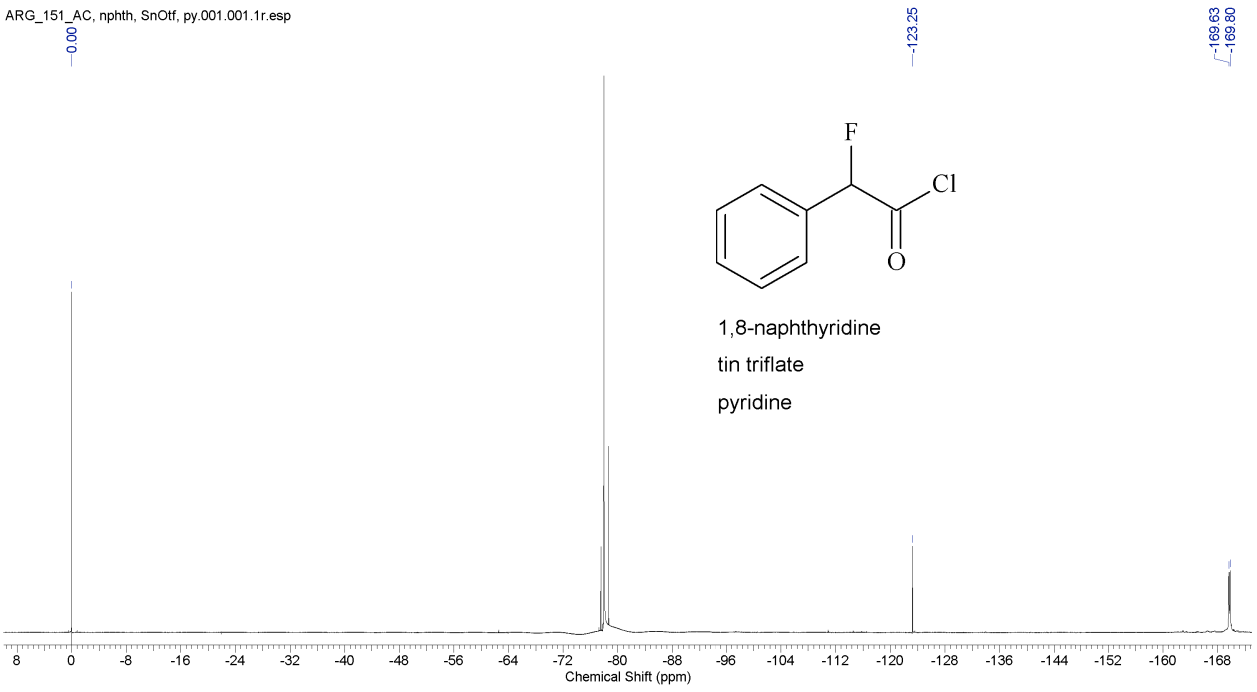


^{19}F NMR Studies for 2-fluoro-2-phenylacetyl chloride




ARG_151_AC,nphth.001.001.1r.esp
0.00
-161.45
-161.61
F
Cl
O
1,8-naphthyridine
8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168
Chemical Shift (ppm)


ARG_151_AC, nphth, SnOtf.001.001.1r.esp
0.00
-161.39
-161.55
F
Cl
O
1,8-naphthyridine
tin triflate
8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168
Chemical Shift (ppm)


ARG_151_AC, nphth, SnOtf, py.001.001.1r.esp
0.00
-123.25
-169.63
-169.80
F
Cl
O
1,8-naphthyridine
tin triflate
pyridine
8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168
Chemical Shift (ppm)

12.3) EXPERIMENTAL DETAILS FOR CHAPTER 4

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditionsunder nitrogen. All solvents and substrates were dried and distilled by standard methods. 1H spectra were acquired on a BRUKER 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a BRUKER 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and or $CFCl_3$ (δ 0.00 ppm). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br m = broad multiplet), integration, coupling constants [Hz]). All measurements were recorded at 25 °C unless otherwise stated. Characterization of 1-fluoroadamantane[250] (**32**), 2- fluoroadamantane[251] (**33**), 1-fluorocyclododecane[252] (**35**), 1-fluorocycloheptane [253] (**36**), 1-fluorocyclooctane[252] (**37**), 1-fluorocyclodecane[253](**38**), monofluorodecalin [254] (**39**), 1-fluorocycloundecane[253] (**40**) monofluorododecane[255] (**41**), (3-fluoroprop-1-en-2-yl)benzene[256] (**42**), 1-[1-

[250] Aoyama, M.; Fukuhara, T.; Hara, S. *J. Org. Chem*. **2008**, *73*, 4186-4189.
[251] Olah, G. A.; Li, X.-Y.; Wang, Q.; Prakash, G. K. S. *Synthesis*, **1993**, *7*, 693-699.
[252] Schneider, H.-J.; Gschwendtner, W.; Heiske, D.; Hoppen, V.; Thomas, F. *Tetrahedron* **1977**, *33*, 1769-1773.
[253] Matsui, T.; Deguchi, M.; Yoshizawa, H. *U.S. Pat. Appl. Publ.* **2005**, US 20050158623 A1 20050721
[254] Chambers, R. D.; Kenwright, A. M.; Parsons, M.; Sandford, G.; Moilliet, J. S. *Perkin Trans. 1* **2002**, *19*, 2190-2197.
[255] Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron*, **2004**, *60*, 6923-6930.
[256] Luo, H.-Q.; Loh, T.-P. *Tetrahedron Lett*. **2009**, *50*, 1554-1556.

(fluoromethyl)ethenyl]-4-methylbenzene[257] (**43**), and 1-(1- fluoroethyl)benzene[258] (**44**) were consistent with literature precedent. Compounds **29**, **33** and **35** are reported as inseparable mixtures. Additional spectral data were processed with ACD/NMR Processor Academic Edition.[259]

Computational Methods:

The Gaussian '09[260] package and Spartan '06 were used for all calculations. Chemical shifts were computed using Gaussian at the B3LYP/6-311++G** level of theory and scaled by 0.9614.12. ^{19}F calculated chemical shifts were fitted to the empirical equation (at B3LYP/6-311^{++}G**) $\delta_{calc} = -0.914\delta + 142.63$. The isotropic values (δ) employed were obtained from the CS GT calculation parameter found in the results menu. Geometry optimizations were likewise determined using the B3LYP/6-311^{++}G** level.

Characterization:

Fluorohexyl acetate (45). Clear oil. ^1H NMR ($CDCl_3$): δ 4.14-4.02 (m, 2H), 2.03 (s, 3H), 1.72-1.50 (m, 2H), 1.34-1.24 (br m, 6H), 1.20-1.01 (m, 1H), 0.90-0.81 (m, 7H); ^{13}C NMR ($CDCl_3$): δ 171.2, 171.0, 64.6, 64.0, 60.3, 41.4, 36.1, 34.1, 31.4, 28.6, 25.6, 22.5, 21.0, 20.9, 19.4, 18.7, 13.9, 11.4; ^{19}F NMR ($CDCl_3$): δ -128.8

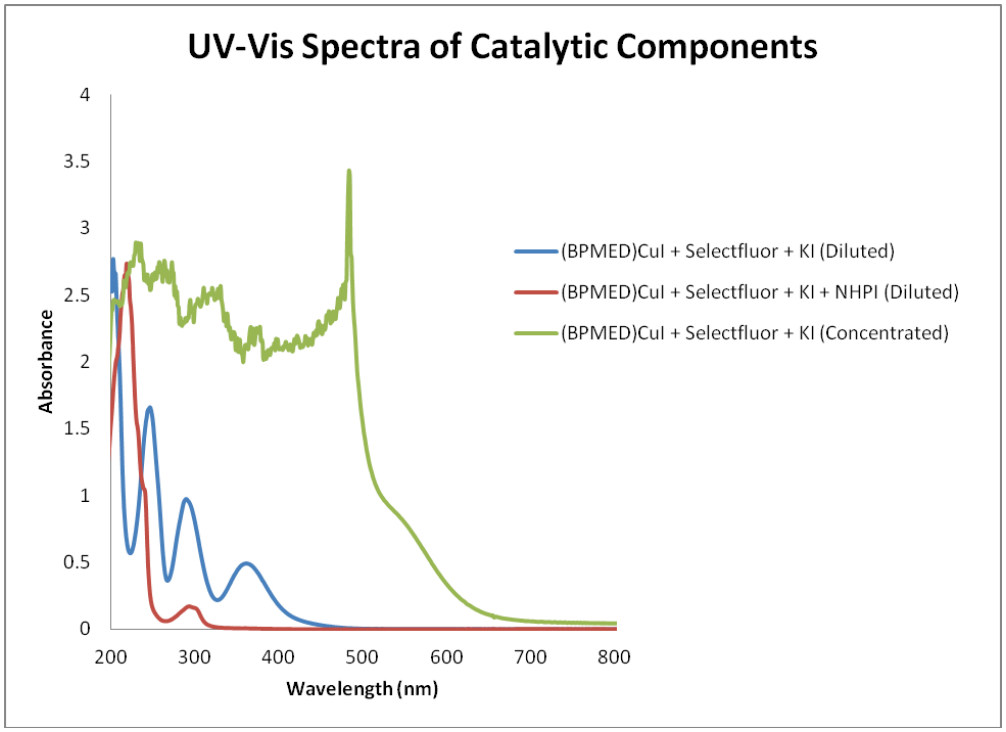
[257] Hu, J.; He, Z. *Faming Zhuanli Shenqing* **2011**, CN102219638
[258] Yin, J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A. *Org. Lett.* **2004**, *6*, 1465-1468.
[259] ACD/NMR Processor Academic Edition, version 12.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, **2012**.
[260] Huczynski, A.; Rutkowski, J.; Brzezinski, B. *Struct. Chem.* **2011**, *22*, 627– 634. 12 Merrick, J. P.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007**, *111*, 11683– 11700.

(m, 1F), -173.0 (m, 1F), -182.3 (m, 1F), -183.5 (m, 1F), -187.1 (m, 1F) consistent with calcd values -175.3 (5-fluorohexylacetate), -182.0 (3-fluorohexylacetate); IR ($CDCl_3$): 1727 cm^{-1}, 1251 cm^{-1}; HRMS-(ESI^+) calcd for $C_8H_{15}FO_2Na^+$: 185.0954, found 185.0943.

Fluoro-dihydrocoumarin (46). Colorless oil. ^1H NMR ($CDCl_3$): δ 7.4-7.0 (m, 4H), 5.70 (dt, 1H. *J* = 50.9 Hz. 3.7 Hz), 3.34-2.95 (dddd, 2H, *J* = 101.2 Hz, 16.8 Hz, 11.4 Hz, 3.6 Hz); ^{19}F NMR ($CDCl_3$): δ -158.5 (m, 1F); HRMS-(ESI^+) calcd for $C_9H_7FO_2Na^+$: 189.0328, found 189.0321. Prone to dehydrofluorination over time.

Fluoroundecanoic δ–lactone (47). Colorless oil. ^1H NMR ($CDCl_3$): δ 4.9-4.0 (m,1H), 2.7-2.2 (m, 1H), 2.0-1.2 (m, 8H). 1.1-0.8 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 171.85, 171.82, 171.76, 171.64, 171.55, 91.55, 80.50, 80.45, 80.33, 79.74, 42.71, 37.47, 37.27, 37.06, 36.86, 36.83, 36.65, 36.62, 35.76, 35.74, 34.91, 34.70, 34.58, 34.37, 34.16, 32.05, 31.73, 31.14, 31.09, 30.93, 30.28, 29.45, 29.43, 29.31, 29.16, 28.05, 27.95, 27.84, 27.83, 27.80, 27.75, 27.44, 27.11, 27.07, 24.93, 24.90, 24.85, 24.78, 24.75, 22.58, 22.46, 21.13, 21.11, 20.90, 20.89, 20.87, 20.82, 18.56, 18.50, 18.45, 18.41, 18.36, 18.29, 14.06, 13.94, 13.90, 9.41, 9.40 ; ^{19}F NMR ($CDCl_3$): δ -172.2 (m, 1F), -173.5 (m, 1F), -181.0 (m, 1F), -181.6 (m, 1F), -184.2 (m, 1F); HRMS-(ESI^+) calcd for $C_{11}H_{19}FO_2Na^+$: 225.1268, found 225.1276.

Fluoro-1,8-dibromooctane (48). Colorless oil. ^{1}H NMR ($CDCl_3$): 4.8-3.9 (m, 1H), 3.7-3.1 (m, 5H), 2.4-1.2 (m, 14H); ^{13}C NMR ($CDCl_3$): δ 94.1, 92.4, 38.7, 38.3, 38.2, 37.3, 34.3, 34.1, 33.9, 33.7, 33.6, 33.5, 33.4, 33.2, 32.4, 32.1, 28.6, 28.4, 28.0, 27.9, 24.2, 23.08, 23.8; ^{19}F NMR ($CDCl_3$): δ -182.1 (m, 1F), -185.5 (m, 2F); HRMS-(ESI$^+$) calcd for $C_8H_{15}Br_2FNa^+$: 310.9418, found 310.9424.



UV-Vis Spectra of Catalytic Components

SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3
Job type: Reading previous wavefunction Program Wall Time: 0:02:03.0 Job type: Geometry optimization. Method: RB3LYP
Basis set: 6-311++G** Number of shells: 135 Number of basis functions: 325 SCF model:
A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization Optimization:
Step Energy Max Grad. Max Dist.

1	-389.9304039	0.005776	0.019012
2	-389.9305001	0.001301	0.002351
3	-389.9304998	0.000561	0.001080
4	-389.9305036	0.000398	0.001080
5	-389.9305046	0.000307	0.001080
6	-389.9305051	0.000245	0.000540

Program Wall Time: 0:35:48.0 Reason for exit: Successful completion
Quantum Calculation CPU Time : 000:37:49.4 SPARTAN '06 Semi-Empirical Program: (PC/x86)
Semi-empirical Property Calculation M001 Guess from Archive
Energy Due to Solvation
Release 129Solvation Energy SM5.4/A -186.668 Memory Used: 1.441 Mb
Reason for exit: Successful completion Semi-Empirical Program CPU Time : .05
SPARTAN '06 Properties Program: (PC/x86) Reason for exit: Successful completion
Properties CPU Time : 1.36
Release 129

SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3
Job type: Reading previous wavefunction Program Wall Time: 0:01:39.0
Job type: Geometry optimization. Method: RB3LYP
Basis set: 6-311++G** Number of shells: 135 Number of basis functions: 325
SCF model: A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-389.9108370	0.015917	0.070275
2	-389.9124129	0.001246	0.003240
3	-389.9124239	0.001123	0.003240
4	-389.9124330	0.001007	0.003240
5	-389.9124396	0.000894	0.003240
6	-389.9124475	0.000780	0.003240
7	-389.9124531	0.000667	0.003240
8	-389.9124585	0.000554	0.001080
9	-389.9124598	0.000516	0.001080
10	-389.9124671	0.000477	0.013433
11	-389.9124694	0.000213	0.000006

Program Wall Time: 0:45:30.0
Reason for exit: Successful completion Quantum Calculation CPU Time : 000:47:05.1
SPARTAN '06 Semi-Empirical Program: (PC/x86) Semi-empirical Property Calculation

M001 Guess from Archive Energy Due to Solvation
Solvation Energy SM5.4/A-194.892
Memory Used: 1.441 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time :.03
SPARTAN '06 Properties Program: (PC/x86) Reason for exit: Successful completion Properties CPU Time : 1.33
Release 129
Release 129

SPARTAN '06 Quantum Mechanics Program: (PC/x86)
Job type: Reading previous wavefunction Program Wall Time: 0:01:35.0 Job type: Geometry optimization.
Method: RB3LYP Basis set: 6-311++G** Number of shells: 141 Number of basis functions: 347 SCF model:
A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization
Release 129v3
Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-564.3702076	0.016099	0.086299
2	-564.3723946	0.008465	0.138994
3	-564.3729860	0.006731	0.082932
4	-564.3731633	0.003046	0.055276
5	-564.3732612	0.002303	0.042155
6	-564.3732830	0.002091	0.052294
7	-564.3733051	0.001085	0.003240
8	-564.3733070	0.000904	0.003240
9	-564.3733107	0.000767	0.003240
10	-564.3733125	0.000641	0.042736
11	-564.3733213	0.000229	0.010015
12	-564.3733216	0.000422	0.003980
13	-564.3733215	0.000162	0.008601

Program Wall Time: 1:07:36.0
Reason for exit: Successful completion
Quantum Calculation CPU Time : 001:09:06.6 SPARTAN '06 Semi-Empirical Program: (PC/x86)
Semi-empirical Property Calculation M001 Guess from Archive Energy Due to Solvation
Solvation Energy SM5.4/A-9.173 Memory Used: 1.668 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time : .05
SPARTAN '06 Properties Program: (PC/x86) Reason for exit: Successful completion Properties CPU Time : 1.53
Release 129

Release 129

SPARTAN '06 MECHANICS PROGRAM: PC/x86
Frequency Calculation Adjusted 3 (out of 78) low frequency modes Reason for exit: Successful completion Mechanics CPU Time : .06
SPARTAN '06 Quantum Mechanics Program: (PC/x86) Job type: Geometry optimization. Method: RB3LYP Basis set: 6-311++G**
Number of shells: 141 Number of basis functions: 347
129
Release 129v3
SCF model: A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-564.3701387	0.017858	0.074355
2	-564.3742751	0.005421	0.027470
3	-564.3745264	0.000708	0.003240
4	-564.3745326	0.000607	0.003240
5	-564.3745351	0.000532	0.001080
6	-564.3745360	0.000517	0.001080
7	-564.3745365	0.000612	0.003240
8	-564.3745369	0.000581	0.001080
9	-564.3745377	0.000574	0.001080
10	-564.3745380	0.000565	0.115075
11	-564.3745489	0.000741	0.021789
12	-564.3745519	0.000411	0.016681
13	-564.3745529	0.000408	0.021727
14	-564.3745537	0.000301	0.014867
15	-564.3745541	0.000305	0.023220
16	-564.3745555	0.000103	0.012058
17	-564.3745561	0.000113	0.002876

Program Wall Time: 1:17:29.0 Reason for exit: Successful completion Quantum Calculation CPU Time : 001:17:23.4
SPARTAN '06 Semi-Empirical Program: (PC/x86) Semi-empirical Property Calculation
M001 Guess from Archive Energy Due to Solvation
Solvation Energy SM5.4/A-10.335 Memory Used: 1.668 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time : .05
SPARTAN '06 Properties Program: (PC/x86)
Reason for exit: Successful completion Properties CPU Time : 1.51

Substrate Reactivity Chart

Decending reactivity	KI	Temperature °C	Time (h)
polycyclic hydrocarbons/adamantane	-	0-25	3
allylics	-	25	overnight to 24
benzylics	-	25	overnight to 24
reactive/strained cycloalkanes	(10 mol%)	81	0.5 to 2
straight chain/functionalized alkanes	~ 1 equiv.	81	1.5 to 5

General comments on reactivity chart: 1) Allylics are not heated as they react to form acetamide derived products easily under these conditions. 2) Decalin will undergo a solvolysis at high temperature, eroding yield somewhat. 3) Functional groups in general are found to slow reactivity.

12.4) EXPPERIMENAL DETAILS FOR CHAPTER 5

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and benzylic compounds were dried and distilled by standard methods. ^{1}H spectra were acquired on a BRUKER 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a BRUKER 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ -64.2 ppm relative to $CFCl_3$).[261] NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]). All measurements were recorded at 25 °C unless otherwise stated. Characterization of 1- (fluoromethyl)-4-isopropylbenzene (**51**),[262] 4-fluorochroman-2-one (**46**),[263] (1-fluoro-2-methylpropyl)benzene (**58**),[264] 4-(fluoromethyl)biphenyl (**59**),[265] and (1-fluoroethyl)benzene (**44**)[266] were consistent with the literature precedents. Crude spectra were collected with a 1 s presaturation pulse on the residual solvent. Spectral data was processed with

[261] Naumann, D.; Kischkewitz, J. *J. Fluorine Chem*. **1990**, *47*, 283-299.
[262] Ramsden, C. A.; Shaw, M. M. *Tetrahedron Lett*. **2009,** *50*, 3321-3324.
[263] Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem. Int. Ed*. **2012,** *51*, 10580- 10583.
[264] Dahbi, A.; Hamman, S.; Beguin, C. G. *Magn. Reson. Chem.* **1986,** *24*, 337-342.
[265] Blessley, G.; Holden, P.; Brown, J. M.; Gouverneur, V.; Walker, M. *Org. Lett*. **2012,** *14*, 2754-2757.
[266] Cazorla, C.; Melay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009,** *50*, 3936-3938.

ACD/NMR Processor Academic Edition.[267]

General Procedure for the Syntheses of Benzylic Fluorinated Products:

An oven-dried, 10 mL round bottom flask equipped with a stir bar was placed under an atmosphere of N2. Selectfluor (195.0 mg, 0.55 mmol, 2.2 equiv) and $Fe(acac)_2$ (6.0 mg, 0.025 mmol, 0.1 equiv) were added followed by MeCN (3.0 mL). 3-phenylpropylacetate (45.0 mg, 0.25 mmol, 1 equiv)) was then added and the mixture allowed to stir overnight. The product was extracted into CH_2Cl_2 and washed with water. The organics were dried with $MgSO_4$ and filtered through celite. The solvents were removed by rotary evaporation and the residue subjected to column chromatography on florisil with a mixture of ethyl acetate/hexanes as eluent.

Computational Methods:

The Gaussian '09[260] package and Spartan '10 were used for all calculations. Chemical shifts were computed using Gaussian at the B3LYP/6-311++G** level of theory and scaled by 0.9614.[268] Geometry optimizations were likewise determined using the B3LYP/6-311++G** level.

Characterization:

3-Phenylpropylacetate (**50**). ^1H NMR ($CDCl_3$): δ 7.43-7.36 (m, 5H), 5.6 (ddd,

[267] ACD/NMR Processor Academic Edition, version 12.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, **2012**.
[268] Merrick, J. P.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007,** *111*, 11683– 11700.

1H, *J* = 47.8, 8.7, 4.3 Hz), 4.33-4.18 (m, 2H), 2.39-2.11 (m, 2H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.8 (s), 139.6 (s), 139.4 (s), 128.5 (s), 125.5 (s), 91.4 (d, *J* = 171 Hz), 60.4 (s), 36.4 (s), 36.1 (s) 20.9 (s); ^{19}F NMR ($CDCl_3$): δ -176.9 (ddd, 1F, *J* = 46.4.9, 29.9, 15.5 Hz); HRMS-(ESI^+) calcd for $C_{11}H_{13}FO_2Na^+$: 219.0798, found 219.0783.

1-(fluoromethyl)-4-isopropylbenzene (51) ^{19}F NMR ($CDCl_3$): -203.1 (t, 1F, *J* = 48.5 Hz).

4-Fluoro-4-phenylbutan-2-one (**52**). ^1H NMR ($CDCl_3$): δ 7.57-7.34 (m, 5H), 5.97 (ddd, 1H, *J* = 46.9, 8.9, 4.1 Hz), 3.21 (ddd, 1H, *J* = 16.8, 14.7, 8.7 Hz), 2.82 (ddd, 1H, *J* = 32.0, 16.8, 4.1 Hz), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 198.4 (s), 143.4 (s), 139.2 (s), 139.0 (s), 134.4 (s), 130.5 (s), 129.0 (s), 128.7 (s) 125.5 (s), 125.4 (s), 90.2 (d, *J* = 171 Hz), 50.8 (s), 50.6 (s), 27.5 (s); ^{19}F NMR (CDCl3): δ -173.6 (ddd, 1F, *J* = 47.4, 32.0, 15.5 Hz); HRMS-(ESI^+) calcd for $C_{10}H_{11}FONa^+$: 189.0692, found 189.0686.

Methyl-2-(4-(1-fluoro-2-methylpropyl)phenyl)propanoate (**53**). ^1H NMR ($CDCl_3$): δ 7.31-7.18 (m, 5H), 5.10 (dd, 1H, *J* = 47.1, 6.8 Hz), 3.73 (q, 1H, *J* = 7.0 Hz), 3.66 (s, 3H), 2.18-1.99 (m, 1H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.02 (dd, 3H, *J* = 6.6, 0.9 Hz), 0.87 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 175.0 (s), 174.9 (s) 140.4 (s), 138.4 (s), 138.2 (s), 130.6 (s), 127.3 (s), 126.5 (s), 99.0 (d, *J* = 175

Hz), 96.3 (s), 52.0 (s), 47.3 (s), 45.2 (s), 45.1 (s), 34.4 (s), 34.1 (s), 26.8 (s), 26.5 (s), 18.6 (s), 18.4 (s), 18.3 (s) 17.6 (s), 17.5 (s); ^{19}F NMR ($CDCl_3$): δ -179.8 (ddd, 1F, *J* = 47.4, 16.5, 6.2 Hz); HRMS-(ESI$^+$) calcd for $C_{14}H_{19}FO_2Na^+$: 261.1267, found 261.1273.

Methyl-3-fluoro-3-phenylpropanoate (**54**). ^1H NMR ($CDCl_3$): δ 7.40-7.34 (m, 5H), 5.90 (ddd, 1H, *J* = 46.7, 9.0, 4.1 Hz), 3.74 (s, 3H), 3.04 (ddd, 1H, *J* = 16.0, 13.6, 9.0 Hz), 2.80 (ddd, 1H, *J* = 32.4, 16.0, 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ 170.0 (s), 138.9 (s), 128.9 (s), 128.7 (s), 125.6 (s), 125.5 (s), 90.6 (d, *J* = 172 Hz), 52.0 (s), 42.4 (s), 42.2 (s); ^{19}F NMR ($CDCl_3$): δ -172.9 (ddd, 1F, *J* = 46.4, 32.0, 13.4 Hz); HRMS-(ESI$^+$) calcd for $C_{10}H_{11}FO_2Na^+$: 205.0641, found 205.0635.

4-fluorochrom-2-one (46) ^1H NMR ($CDCl_3$): δ 7.48-7.03 (m, 4H), 5.7 (dt, 1H, *J* = 50.9, 3.7 Hz), 3.37- 2.96 (m, 2H); ^{19}F NMR (CDCl3): δ -158.5 (ddd, 1F, *J* = 50.5, 38.1, 11.34 Hz).

3-Fluoro-1,3-diphenylpropan-1-one (**55**). ^1H NMR ($CDCl_3$): δ 8.10-7.30 (m, 10H), 6.21 (ddd, 1H, *J* = 46.5, 8.3, 4.1 Hz), 3.83 (ddd, 1H, *J* = 17.0, 14.9, 8.3), 3.35 (ddd, 1H, *J* = 29.6, 17.0, 4.1); ^{13}C NMR ($CDCl_3$): δ 190.6 (s), 144.8 (s), 139.7 (s), 139.4 (s), 136.7 (s), 133.5 (s), 132.8 (s), 130.5 (s), 129.0 (s), 128.7 (s), 128.2 (s), 125.7 (s), 125.6 (s), 122.2 (s), 90.3 (d, *J* = 170 Hz), 46.2 (s), 45.8 (s); ^{19}F NMR ($CDCl_3$): δ -173.0 (ddd, 1F, *J* = 46.4, 29.9, 15.5 Hz); HRMS-(ESI$^+$) calcd

for $C_{15}H_{13}FONa^+$: 251.0848, found 251.0853.

3-Fluoro-3-phenyl-1-(pyrrolidin-1-yl)propanoate (**56**). ^1H NMR ($CDCl_3$): δ 7.42-7.20 (m, 5H), 6.03 (ddd, 1H, *J* = 47.1, 9.0, 3.6 Hz), 4.13-4.04 (m, 1H), 3.73-3.56 (m, 1H), 3.23-3.11 (m, 1H), 3.01-2.96 (m, 1H), 2.86-2.67 (m, 1H), 1.81-1.60 (m, 6H), 1.44-1.06 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 206.9 (s), 153.9 (s), 153.5 (s), 140.9 (s), 139.0 (s), 138.8 (s), 128.7 (s), 128.6 (s), 125.5 (s), 125.4 (s), 91.9 (d, *J* = 172 Hz), 55.2 (s), 50.1 (s), 49.8 (s), 43.5 (s), 43.2 (s), 37.5 (s), 32.8 (s), 32.6 (s), 32.5 (s), 30.9 (s), 29.7 (s), 26.3 (s), 26.1 (s), 25.3 (s), 24.7 (s); ^{19}F NMR ($CDCl_3$): δ -172.8 (ddd, 1F, *J* = 46.4, 34.0, 12.4 Hz); HRMS-(ESI^+) calcd for $C_{13}H_{16}FNONa^+$: 244.1114, found 244.1109.

(3-Bromo-1-fluoropropyl)benzene (**57**) ^1H NMR ($CDCl_3$): δ 7.41-7.24 (m, 5H), 5.60 (ddd, 1H, *J* = 47.9, 8.9, 3.4 Hz), 3.59-3.51 (m, 1H), 3.45-3.38 (m, 1H), 2.75 (t, 2H, *J* = 7.3 Hz), ^{13}C NMR ($CDCl_3$): δ 140.3 (s), 139.0 (s), 138.7 (s), 128.6 (s), 128.4 (s), 128.3 (s), 126.4 (s), 125.9 (s), 125.3 (s), 125.2 (s), 116.2 (s), 91.9 (d, *J* = 172 Hz), 40.1 (s), 39.7 (s), 33.9 (s), 33.7 (s), 32.9 (s), 28.3 (s), 28.2 (s); ^{19}F NMR ($CDCl_3$): δ -178.6 (ddd, 1F, *J* = 48.5, 30.9, 14.4 Hz); HRMS-(ESI^+) calcd for $C_9H_{10}BrFNa^+$: 238.9848, found 238. 9854.

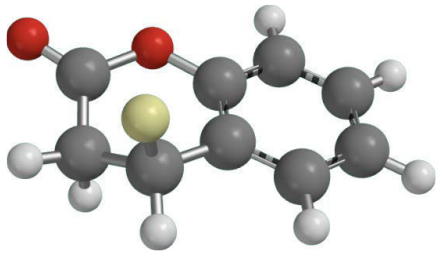
(1-fluoro-2-methylpropyl)benzene (58) ^1H NMR ($CDCl_3$): δ 7.41-7.20 (m, 5H), 5.1 (dd, 1H, *J* = 46.9, 6.6 Hz), 2.19-2.02 (m, 1H), 1.02 (dd, 3H, *J* = 6.6, 0.9 Hz);

0.85 (d, 3H, J = 6.8 Hz); ^{19}F NMR ($CDCl_3$): δ - 179.4 (dd, 1F, J = 47.4, 17.5 Hz).

4-(fluoromethyl)biphenyl (59) ^{1}H NMR ($CDCl_3$): δ 7.74-7.66 (m, 4H), 7.55-7.47 (m, 4H), 7.44-7.38 (m, 1H), 5.5 (d, 2H, J = 47.5 Hz); ^{19}F NMR ($CDCl_3$): δ -205.2 (t, 1F, J = 47.4 Hz).

(1-fluoroethyl)benzene (44) ^{1}H NMR ($CDCl_3$): δ 7.40-7.16 (m, 5H), 5.6 (dq, 1H, J = 47.9, 6.6 Hz), 1.49- 1.24 (m, 3H); ^{19}F NMR ($CDCl_3$): δ -166.3 (dq, 1F, J = 47.4, 23.7 Hz).

(1-Fluoroheptyl)benzene (**60**). ^{1}H NMR ($CDCl_3$): δ 7.42-7.19 (m, 13H), 6.42-6.22 (m, 1H), 5.44 (ddd, 1H, J = 48.0, 8.1, 5.1 Hz), 2.98-2.65 (m, 1H), 2.26-2.20 (m, 1H), 2.07-1.92 (m, 1H), 1.92-1.75 (m, 1H), 1.74-1.59 (m, 1H), 1.54-1.45 (m, 3H), 1.42-1.29 (m, 12H), 0.95-0.89 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 140.7 (s), 131.3 (s), 128.5 (s), 128.4 (s), 126.8 (s), 125.9 (s), 125.6 (s), 125.5 (s), 94.7 (d, J = 170 Hz), 45.1 (s), 33.0 (s), 31.7 (s), 31.4 (s), 29.0 (s), 25.1 (s), 22.6 (s), 14.1 (s); ^{19}F NMR ($CDCl_3$): δ -173.6 (ddd, 1F, J = 46.4, 27.8, 16.5 Hz); HRMS-(ESI^{+}) calcd for $C_{13}H_{19}FNa^{+}$: 217.1369, found 217.1364.

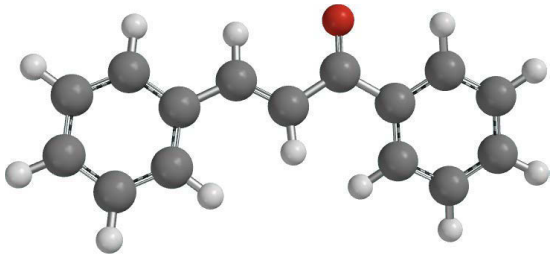


MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4 Job type: Reading previous wavefunction Job type: Geometry optimization.

Method: RB3LYP Basis set: 6-311++G** Number of shells: 107 Number of basis functions: 313 Multiplicity: 1 Parallel Job: 6 threads SCF model: A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization Optimization:

Step	Energy Max	Grad.	Max Dist.
1	-597.636664	0.015177	0.133183
2	-597.639414	0.004703	0.138833
3	-597.639681	0.003471	0.010783
4	-597.639760	0.001002	0.014092
5	-597.639773	0.000568	0.013874
6	-597.639780	0.000219	0.010909
7	-597.639782	0.000106	0.003895
8	-597.639783	0.000045	0.001266
9	-597.639781	0.000028	0.000788

Reason for exit: Successful completion Quantum Calculation CPU Time : 18:27.92 Quantum Calculation Wall Time: 20:47.62 MacSPARTAN '10 Semi-Empirical Program: (x86/Darwin) build 1.1.0 Semi-empirical Property Calculation M0001 Guess from Archive Energy Due to Solvation Solvation Energy SM5.4/A -20.767 Memory Used: 1.230 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time : .04 Semi-Empirical Program Wall Time: .05 MacSPARTAN '10 Properties Program: (x86/Darwin) build 1.1.0 Reason for exit: Successful completion Properties CPU Time : 1.47 Properties Wall Time: 1.49 molecule M0001 terminated normally

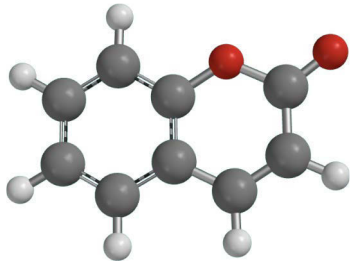


MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4 Job type: Reading previous wavefunction Job type: Geometry optimization.
Method: RB3LYP Basis set: 6-311++G** Number of shells: 156 Number of basis functions: 436 Multiplicity: 1 Parallel Job: 6 threads SCF model: A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-654.204304	0.026882	0.214048
2	-654.199541	0.062871	0.166719
3	-654.207356	0.006528	0.171666
4	-654.207384	0.007494	0.062019
5	-654.207644	0.001140	0.029517

6	-654.207645	0.000561	0.008737
7	-654.207651	0.000322	0.016869
8	-654.207657	0.000249	0.012771
9	-654.207661	0.000206	0.012616
10	-654.207663	0.000162	0.010503
11	-654.207663	0.000118	0.004481

Reason for exit: Successful completion Quantum Calculation CPU Time : 42:52.72 Quantum Calculation Wall Time: 45:50.65 MacSPARTAN '10 Semi-Empirical Program: (x86/Darwin) build 1.1.0 Semi-empirical Property Calculation M0001 Guess from Archive Energy Due to Solvation Solvation Energy SM5.4/A -16.841 Memory Used: 2.739 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time : .06 Semi-Empirical Program Wall Time: .09 MacSPARTAN '10 Properties Program: (x86/Darwin) build 1.1.0 Reason for exit: Successful completion Properties CPU Time : 2.90 Properties Wall Time: 2.98

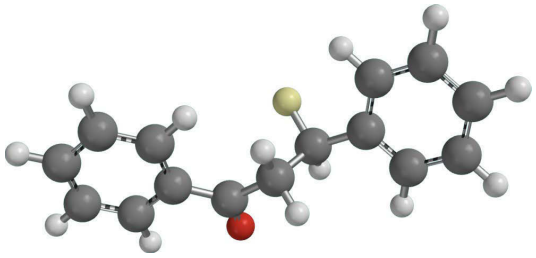


MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4 Job type: Reading previous wavefunction Job type: Geometry optimization.
Method: RB3LYP Basis set: 6-311++G** Number of shells: 96 Number of basis functions: 284 Multiplicity: 1 Parallel Job: 6 threads SCF model: A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-497.154571	0.022530	0.059282
2	-497.156760	0.005105	0.011194
3	-497.156938	0.001394	0.003240
4	-497.156950	0.000654	0.002385
5	-497.156953	0.000118	0.000310

Reason for exit: Successful completion Quantum Calculation CPU Time : 8:04.16 Quantum Calculation Wall Time: 9:38.72 MacSPARTAN '10 Semi-Empirical Program: Semi-empirical Property Calculation M0001
Direct Minimization
(x86/Darwin) build 1.1.0
Guess from Archive Energy Due to Solvation Solvation Energy SM5.4/A -20.217 Memory Used: 0.981 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time : .04 Semi-Empirical Program Wall Time: .05 MacSPARTAN '10 Properties Program: (x86/Darwin) build 1.1.0 Reason for exit: Successful

completion Properties CPU Time : 1.35 Properties Wall Time: 1.38 molecule M0001 terminated normally



MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4 Job type: Reading previous wavefunction Job type: Geometry optimization.
Method: RB3LYP Basis set: 6-311++G** Number of shells: 167 Number of basis functions: 465 Multiplicity: 1 Parallel Job: 6 threads SCF model: A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-754.693547	0.022656	0.094203
2	-754.697691	0.007810	0.134000
3	-754.698236	0.004072	0.079592
4	-754.698552	0.002787	0.026130
5	-754.698654	0.001424	0.026589
6	-754.698698	0.000645	0.045602
7	-754.698744	0.000586	0.128993

sp_qchem (6463) returned error status of 3 Task "Q-CHEM" returned [3] End-molecule "M0001" Fri Feb 8 17:29:07 2013 MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4 Job type: Reading previous wavefunction Job type: Geometry optimization. Method: RB3LYP Basis set: 6-311++G** Number of shells: 167 Number of basis functions: 465 Multiplicity: 1 Parallel Job: 6 threads SCF model: A restricted hybrid HF-DFT SCF calculation will be performed using Pulay DIIS + Geometric Direct Minimization Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-754.698859	0.001463	0.003240
2	-754.698865	0.001465	0.003240
3	-754.698867	0.001361	0.003240
4	-754.698878	0.001283	0.083028
5	-754.698926	0.001312	0.019437
6	-754.698927	0.001878	0.010827
7	-754.698946	0.000635	0.011129
8	-754.698952	0.000686	0.018319
9	-754.698959	0.000456	0.030542
10	-754.698965	0.000541	0.006447
11	-754.698966	0.000271	0.006938
12	-754.698968	0.000139	0.007594

13 -754.698969 0.000101 0.001795
Reason for exit: Successful completion Quantum Calculation CPU Time : 1:02:01.37 Quantum Calculation Wall Time: 1:06:47.35 MacSPARTAN '10 Semi-Empirical Program: (x86/Darwin) build 1.1.0 Semi-empirical Property Calculation M0001 Guess from Archive Energy Due to Solvation Solvation Energy SM5.4/A -15.825 Memory Used: 3.208 Mb Reason for exit: Successful completion Semi-Empirical Program CPU Time : .07 Semi-Empirical Program Wall Time: .11 MacSPARTAN '10 Properties Program: (x86/Darwin) build 1.1.0 Reason for exit: Successful completion Properties CPU Time : 3.51 Properties Wall Time: 3.53 molecule M0001 terminated normally

12.5) EXPERIMENTAL DETAILS FOR CHAPTER 6

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and benzylic compounds were dried and distilled by standard methods. ^{1}H spectra were acquired on a 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ –64.2 ppm relative to CFCl3). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]). IR data were obtained using an FT-IR and standard NaCl cell. High resolution mass spectra (HRMS) were recorded using ESI-TOF (electrospray ionization-time-of-flight) mass spectrometry. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 3- fluoro-3-phenylpropanenitrile **(63)**, [269] methyl-3-fluoro-2-methyl-3-phenylpropanoate **(70)**,[270] and 3-fluoro-1,3-diphenylpropan-1-one **(55)** [103] were consistent with the literature precedents. Spectral data was processed with ACD/NMR Processor Academic Edition.[267]

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[269] Guolin, C.; Chan, J. N.; Dominguez, C.; Lu, Y.; Rishton, G. M. Patent US2003/195221 AI, **2003**.
[270] Ayi, A.; Remli, M.; Guedj, R. *J. Fluorine Chem*. **1981,** *17*, 127-144.

General Procedure for the Syntheses of β-Fluorinated Products:

An oven-dried, 10-mL, round-bottom flask equipped with a stir bar was placed under an atmosphere of N2. Selectfluor (195.0 mg, 0.55 mmol, 2.2 equiv) and Fe(acac)2 (6.0 mg, 0.025 mmol, 0.1 equiv) were added followed by MeCN (3.0 mL). 3-Phenylpropiononitrile (32.8 mg, 0.25 mmol, 1 equiv) was then added, and the mixture allowed to stir overnight. The product was extracted into CH2Cl2 and washed with water. The organics were dried with MgSO4 and filtered through Celite. The solvents were removed by rotary evaporation, and the residue was subjected to column chromatography on silica with a mixture of ethyl acetate/hexanes as eluent to afford 3- fluoro-3-phenylpropanenitrile as a clear oil (16.4 mg, 44%).

Computational Methods:

The Gaussian 09[260] package and Spartan '10 were used for all calculations. Chemical shifts of the products were computed using Gaussian at the B3LYP/6-311^{++}G** level. Geometry optimizations of organocopper complexes were determined at the B3LYP/6-31G* (LANL2DZ on Cu) level.

Characterization.

3-Fluoro-3-phenylpropanenitrile (63). Spectral and analytical data were in agreement with previous reports.[269] Yield: (16.4 mg, 44%).

3-Fluoro-3-phenylpropanoic Acid (64). Amorphous solid; ^{1}H NMR (CDCl3) δ 7.46–7.40 (m, 5H), 5.95 (ddd, 1H, *J* = 46.7, 9.0, 4.0 Hz), 3.12 (ddd, 1H, *J* = 25.4, 16.4, 8.9 Hz), 2.89 (ddd, 1H, *J* = 32.4, 16.2, 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 177.5 (s), 138.4 (d, *J* = 19.0 Hz), 128.9 (s), 128.7 (s), 128.4 (d, *J* = 30.7 Hz), 126.4 (s), 125.6 (d, *J* = 5.9 Hz), 90.4 (d, *J* = 172.7 Hz), 30.2 (d, *J* = 90.0 Hz); ^{19}F NMR ($CDCl_3$) δ −172.4 (ddd, 1F, *J* = 45.4, 33.0, 13.4 Hz); IR (CH_2Cl_2) 3065, 1717 cm^{-1}; HRMS (ESI^+) calcd for $C_9H_9FO_2Na^+$ 191.0485, found 191.0491. Yield: (20.2 mg, 48%).

3-Fluoro-3-(4-isopropylphenyl)-2-methylpropanal (65). Clear oil; ^{1}H NMR ($CDCl_3$) δ 9.90 (dd, 1H, *J* = 2.2, 0.9 Hz), 9.76 (t, 1H, *J* = 1.2 Hz), 7.50–7.10 (m, 8H), 5.87 (dd, 1H, *J* = 46.7, 4.7 Hz), 5.57 (dd,1H, *J* = 46.5, 8.3 Hz), 3.10–2.75 (m, 4H), 1.25 (d, 6H, *J* = 7.0 Hz), 1.25 (d, 6H, *J* = 8.3 Hz), 1.17 (dd, 3H, *J* = 7.2, 0.8 Hz), 0.96 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (CDCl3) δ 202.2 (d, *J* = 3.7 Hz), 201.8 (d, *J* = 4.4 Hz), 195.6 (s), 150.92 (s), 150.0 (s), 149.4 (s), 137.6 (s), 134.9 (d, *J* = 20.5 Hz), 134.4 (d, *J* = 20.5 Hz), 130.3 (s), 126.9 (s), 126.8 (s), 126.7 (s), 126.4 (s), 126.4 (s), 125.6 (s), 125.5 (s), 94.6 (d, *J* = 172.6 Hz), 92.6 (d, *J* = 176.4 Hz), 52.5 (d, *J* = 23.4 Hz), 52.0 (d, *J* = 23.4 Hz), 34.1 (s), 33.9 (d, *J* = 4.4 Hz), 23.9 (s), 23.8 (s), 13.3 (s), 11.0 (s), 10.4 (d, *J* = 6.6 Hz), 8.07 (d, *J* = 5.1 Hz; ^{19}F NMR ($CDCl_3$) δ −171.5 (dd, 1F, *J* = 47.4, 15.5 Hz), δ −186.9 (dd, 1F, *J* = 46.4, 24.7 Hz); IR (CH_2Cl_2) 1679 cm^{-1}; HRMS (ESI^+) calculated for $C_{13}H_{17}FONa^+$ 231.1161, found 231.1169. Yield: (34.9 mg, 67%).

(1-Fluoro-2-(phenylsulfonyl)ethyl)benzene (66). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ 8.0–7.63 (m, 10H), 6.11 (ddd, 1H, *J* = 47.5, 9.4, 2.5 Hz), 3.83 (ddd, 1H, *J* = 22.8, 13.4, 1.7 Hz), 3.49 (ddd, 1H, *J* = 31.7, 15.3, 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 139.1 (s), 137.5 (s), 133.9 (s), 133.8 (s), 129.4 (s), 129.3 (s), 128.9 (s), 128.8 (s), 128.3 (s), 128.1 (s), 126.9 (s), 125.5 (d, *J* = 6.6 Hz), 88.5 (d, *J* = 177.1 Hz), 62.7 (d, *J* = 26.4 Hz); ^{19}F NMR ($CDCl_3$) δ –172.1 (ddd, 1F, *J* = 46.4, 32.0, 13.4 Hz); IR (CH_2Cl_2) 1087, 1151 cm^{-1}; HRMS (ESI^+) calcd for $C_{14}H_{13}FO_2SNa^+$ 287.0518, found 287.0512. Yield: (29.7 mg, 45%).

1-Fluoro-1,5-diphenylpentan-3-one (67). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ 7.45–7.15 (m, 10H), 6.01 (ddd, 1H, *J* = 46.9, 8.9, 4.1 Hz), 3.2 (ddd, 1H, *J* = 14.7, 8.3, 2.5 Hz), 3.0–2.7 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 205.8 (s), 142.6 (s), 140.7 (s), 139.2 (s), 139.0 (s), 128.9 (s), 128.7 (s), 128.6 (s), 128.5 (s), 128.3 (s), 126.2 (s), 125.5 (s), 25.4 (s), 90.1 (d, *J* = 165 Hz), 50.1 (d, *J* = 25.6 Hz), 42.2 (s), 29.4 (s); ^{19}F NMR ($CDCl_3$) δ –173.4 (ddd, 1F, *J* = 7.4, 32.0, 14.4 Hz); IR (CH_2Cl_2) 1715 cm^{-1}; HRMS (ESI^+) calcd for $C_{17}H_{17}FONa^+$ 279.1161, found 279.1168. yield: (35.9 mg, 56%).

3-(3-Fluoro-3-phenylpropanoyl)oxazolidin-2-one (68). Amorphous solid; ^{1}H NMR $CDCl_3$) δ 7.47–7.35 (m, 5H), 6.05 (ddd, 2H, *J* = 47.1, 9.0, 3.4 Hz), 4.49–4.39 (m, 2H), 4.16–4.0 (m, 2H), 3.8 (ddd, 1H, *J* = 16.7, 9.2, 3.0 Hz), 3.36 (ddd, 1H, *J* = 32.8, 16.7, 3.4 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3 (s), 153.5 (s), 138.7

(d, J = 19.8 Hz), 128.8 (d, J = 2.2 Hz), 128.6 (s), 128.5 (d, J = 8.0 Hz), 125.7 (d, J = 6.6 Hz), 90.0 (d, J = 172 Hz), 62.2 (s), 42.8 (d, J = 27.1 Hz), 42.5 (s); ^{19}F NMR ($CDCl_3$) δ −173.6 (ddd, 1F, J = 47.4, 33.0, 13.4 Hz); IR (CH_2Cl_2) 1706, 1783 cm^{-1}; HRMS (ESI^+) calcd for $C_{12}H_{12}FNO_3Na^+$ 260.0699, found 260.0691. Yield: 30.2 mg, 51%).

2-(Fluoro(phenyl)methyl)cyclohexanone (69). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.56–7.25 (m, 10H), 6.09 (dd, 1H, J = 46.5, 4.1 Hz), 5.87 (dd, J = 45.2, 7.7 Hz), 3.26–1.52 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 209.9 (d, J = 2.9 Hz), 209.4 (d, J = 2.9 Hz), 139.2 (d, J = 20.5 Hz), 137.6 (d, J = 20.5 Hz), 130.3 (s), 128.6 (d, J = 2.9 Hz), 128.4 (s), 128.3 (s), 128.1 (s), 128.0 (d, J = 1.5 Hz), 126.6 (d, J = 7.3 Hz), 125.5 (d, J = 8.0 Hz), 92.3 (d, J = 174.2 Hz), 90.8 (d, J = 170.5 Hz), 56.3 (d, J = 5.1 Hz), 56.1 (d, J = 5.9 Hz), 42. Three (s), 29.9 (d, J = 5.1 Hz), 28.1 (s), 27.5 (s), 27.2 (s), 26.6 (d, J = 5.9 Hz), 24.5 (d, J = 2.2 Hz), 23.8 (s); ^{19}F NMR ($CDCl_3$) δ −96.9 (dd, J = 1492.9, 12.4 Hz), −95.2 (dd, J = 990.8, 12.4 Hz), −172.3 (dd, 1F, J = 45.4, 15.5 Hz), −191.6 (dd, 1F, J = 45.4, 21.7 Hz); IR (CH_2Cl_2) 1721 cm^{-1}; HRMS (ESI^+) calcd for $C_{13}H_{15}FONa^+$ 229.1005, found 229.1009.HRMS (ESI^+) Yield: (28.9 mg, 56%).

Methyl 3-Fluoro-2-methyl-3-phenylpropanoate (70). Spectral and analytical data were in agreement with previous reports.[270] Yield: (33.8 mg, 69%).

2-Phenylpropyl 3-Fluoro-3-phenylpropanoate (71). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.44–7.20 (m, 20H), 5.97–5.80 (m, 2H), 4.40– 4.20 (m, 4H), 3.25–2.65 (m, 6H), 1.33 (d, 3H, J = 0.8 Hz), 1.31 (d, 3H, J = 0.8); ^{13}C NMR ($CDCl_3$) δ 169.5 (s), 142.9 (d, J = 2.2 Hz), 138.6 (d, J = 19.8 Hz), 128.8 (d, J = 2.2 Hz), 128.7 (s), 128.5 (d, J = 1.5 Hz), 127.3 (s), 126.8 (d, J = 1.5 Hz), 125.6 (dd, J = 6.6, 2.2 Hz), 90.6 (d, J = 171.3 Hz), 69.9 (d, J = 4.4 Hz), 42.4 (dd, J = 28.5, 2.9 Hz), 38.9 (s), 17.7 (s); ^{19}F NMR ($CDCl_3$) δ –172.2 (m, 1F); IR (CH_2Cl_2) 1738 cm^{-1}; HRMS (ESI^+) calcd for $C_{18}H_{19}FO_2Na^+$ 309.1267, found 309.1272. Yield: (41.5 mg, 58%).

3-Fluoro-1,3-diphenylpropan-1-one (55). Spectral and analytical data were in agreement with previous reports.[114] Yield: (34.8 mg, 61%).

Methyl 1-Fluoro-2,3-dihydro-1H-indene-2-carboxylate (72). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.55–7.28 (m, 7H), 7.28–7.15 (m, 1H), 6.31 (dd, 1H, J = 56.3, 5.1 Hz), 6.06 (dd, 1H, J = 56.9, 4.7 Hz) 3.84 (s, 3H), 3.80 (s, 3H), 3.73–3.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.2 (d, J = 5.9 Hz), 170.5 (d, J = 3.7 Hz), 156.6 (s), 143.9 (d, J = 5.1 Hz), 141.5 (t, J = 5.9 Hz), 138.8 (d, J = 19.0 Hz), 138.0 (d, J = 16.1Hz), 130.7 (d, J = 4.4 Hz), 130.0 (d, J = 2.9 Hz), 127.3 (dd, J = 18.3, 2.9 Hz), 126.0 (d, J = 2.9 Hz), 125.1 (dd, J = 41.7, 1.5 Hz), 125.2 (d, J= 2.9 Hz), 124.3 (s), 98.1 (d, J = 180.8 Hz), 95.5 (d, J = 178.6 Hz), 52.3 (d, J = 19.0 Hz), 50.9 (d, J = 21.9 Hz), 49.7 (d, J = 23.4 Hz), 43.5 (s), 36.2 (s), 32.9 (dd, J = 144.9, 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ –163.9 (dd, 1F, J = 58.8, 24.7 Hz), –167.0 (dd, 1F, J = 55.7, 30.9 Hz);

IR (CH2Cl2) 1740 cm^{-1}; HRMS (ESI^+) calcd for $C_{11}H_{11}FO_2Na^+$ 217.0641, found 217.0637. Yield: (34.5 mg, 71%).

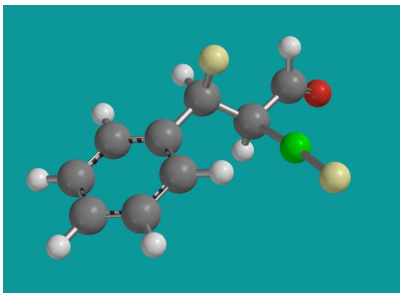
Methyl 3-Fluoro-2,3-diphenylpropanoate (73). Clear oil; ^1H NMR ($CDCl_3$) δ 7.50–7.08 (m, 20H), 6.11–5.90 (m, 2H), 4.18–4.06 (m, 2H), 3.83 (s, 4H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 171.9 (s), 170.9 (s), 137.9 (s), 137.7 (s), 136.9 (s), 136.6 (s), 134.6 (s), 133.4 (s), 133.3 (s), 128.9 (d, *J* = 23.0 Hz), 128.7 (d, *J* = 24.2 Hz), 128.3 (s), 128.1 (s), 126.7 (m), 92.8 (d, *J* = 178.4 Hz), 92.3 (d, *J* = 177.8 Hz), 58.7 (d, *J* = 26.9 Hz), 52.5 (s), 52.3 (s); ^{19}F NMR: –167.6 (dd, 1F, *J* = 45.4, 8.3 Hz), –178.2 (dd, 1F, *J* = 46.4, 13.4 Hz); IR (CH_2Cl_2) 1737 cm^{-1}; HRMS (ESI^+) calcd for $C_{16}H_{15}FO_2Na^+$ 281.0954, found 281.0959. Yield: (48.4 mg, 75%).

Ethyl-3-(4-chlorophenyl)-3-fluoropropanoate (74). Spectral and analytical data were in agreement with previous reports.[271] Yield: (21.9 mg, 38%).

Ethyl-3-(3-methoxyphenyl)-3-fluoropropanoate (75). Spectral and analytical data were in agreement with previous reports.[271] Yield: (24.3 mg, 43%).

Ethyl-3-(4-bromophenyl)-3-fluoropropanoate (76). Spectral and analytical data were in agreement with previous reports.[271] Yield: (27.5 mg, 40%).

[271] (a) Ayi, A.; Condom, R.; Wade, T. N.; Guedj, R. *J. Fluorine Chem.* **1979,** *14*, 437-454. (b) Ayi, A,; Condom, R.; Maria, P. C.; Wade, T. N.; Guedj, R. *Tetrahedron* **1978,** *19*, 4507-4510.



MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4
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Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-31G(D)
Number of shells: 71
Number of basis functions: 225
Charge : -1
Multiplicity: 1
Parallel Job: 6 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

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3	-2263.031684	0.011337	0.131702
4	-2263.030781	0.019903	0.096202
5	-2263.033133	0.008331	0.184237
6	-2263.033427	0.011310	0.113859
7	-2263.034826	0.010962	0.105684
8	-2263.035646	0.007770	0.106678
9	-2263.036317	0.007974	0.118612
10	-2263.037802	0.004889	0.113433
11	-2263.039135	0.007312	0.127293
12	-2263.040452	0.010822	0.111535
13	-2263.041495	0.008832	0.087810
14	-2263.042464	0.013089	0.126370
15	-2263.043829	0.005984	0.114218
16	-2263.044608	0.004500	0.063762
17	-2263.044803	0.002110	0.020123
18	-2263.044859	0.001867	0.014661
19	-2263.044900	0.000853	0.025496
20	-2263.044934	0.000678	0.018275
21	-2263.044948	0.000539	0.008059

22	-2263.044959	0.000704	0.010507
23	-2263.044971	0.000730	0.014961
24	-2263.044983	0.001030	0.019149
25	-2263.044997	0.000749	0.020978
26	-2263.045008	0.000526	0.009691
27	-2263.045014	0.000362	0.003005
28	-2263.045015	0.000183	0.001716
29	-2263.045016	0.000189	0.002929

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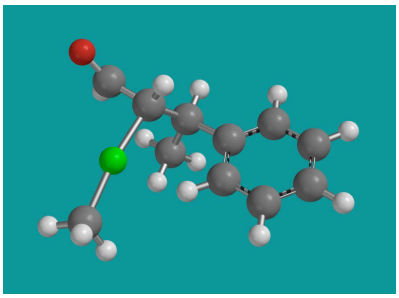

MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4
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Job type: Geometry optimization.
Method: RB3LYP
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Number of shells: 83
Number of basis functions: 237
Charge : -1
Multiplicity: 1
Parallel Job: 6 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

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3	-2143.132545	0.024011	0.096578

4	-2143.133520	0.026555	0.124204
5	-2143.131576	0.039699	0.101868
6	-2143.134366	0.024856	0.122694
7	-2143.135381	0.014473	0.089904
8	-2143.134164	0.018920	0.096869
9	-2143.137182	0.012913	0.102917
10	-2143.134992	0.020996	0.126059
11	-2143.135531	0.024697	0.118094
12	-2143.136045	0.014470	0.103220
13	-2143.135856	0.018089	0.097854
14	-2143.136387	0.018151	0.112556
15	-2143.137679	0.019860	0.088381
16	-2143.138365	0.013168	0.102260
17	-2143.139017	0.013048	0.079493
18	-2143.138825	0.015186	0.072761
19	-2143.139378	0.013517	0.095504
20	-2143.138535	0.012775	0.091743
21	-2143.139394	0.013429	0.090857
22	-2143.138273	0.014272	0.086753
23	-2143.139489	0.012379	0.093745
24	-2143.139140	0.012875	0.070464
25	-2143.140975	0.005844	0.075861
26	-2143.140745	0.007051	0.133612
27	-2143.141329	0.002706	0.132371
28	-2143.140744	0.006861	0.092457
29	-2143.141466	0.001274	0.239000
30	-2143.141467	0.001715	0.161646
31	-2143.141552	0.001927	0.233558
32	-2143.141612	0.001823	0.271473
33	-2143.141723	0.001704	0.269976
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35	-2143.141855	0.000539	0.270805
36	-2143.141899	0.000440	0.270778
37	-2143.141931	0.000589	0.270929
38	-2143.141950	0.000806	0.233462
39	-2143.141958	0.000418	0.133845
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43	-2143.141986	0.000226	0.072163
44	-2143.141990	0.000242	0.098378
45	-2143.141995	0.000263	0.136283
46	-2143.142001	0.000426	0.084265
47	-2143.142008	0.000265	0.058689

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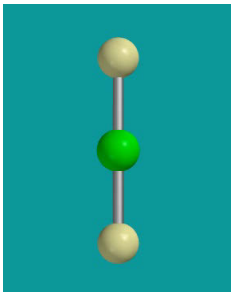

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Frequency Calculation
Reason for exit: Successful completion
Mechanics CPU Time : .04
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Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-31G(D)
Number of shells: 15
Number of basis functions: 59
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Multiplicity: 1
Parallel Job: 6 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
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Reason for exit: Successful completion
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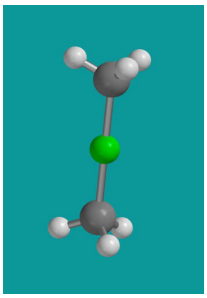

MacSPARTAN '10 MECHANICS PROGRAM: x86/Darwin 1.1.0
Frequency Calculation
Adjusted 1 (out of 27) low frequency modes
Reason for exit: Successful completion
Mechanics CPU Time : .07
Mechanics Wall Time: .17
MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-31G(D)
Number of shells: 27
Number of basis functions: 71
Charge : -1
Multiplicity: 1
Parallel Job: 6 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
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3	-1720.096572	0.003202	0.018017

4	-1720.096631	0.000715	0.006738
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Reason for exit: Successful completion
Quantum Calculation CPU Time : 14.49
Quantum Calculation Wall Time: 24.89
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Reason for exit: Successful completion
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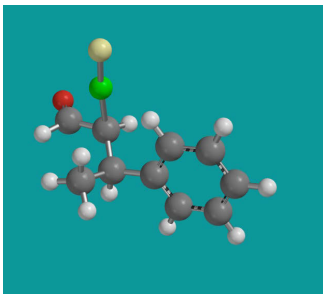

MacSPARTAN '10 MECHANICS PROGRAM: x86/Darwin 1.1.0
Frequency Calculation
Adjusted 2 (out of 72) low frequency modes
Reason for exit: Successful completion
Mechanics CPU Time : .06
Mechanics Wall Time: .24
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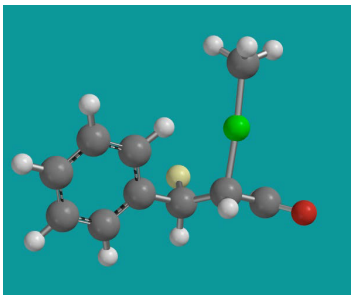
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-31G(D)
Number of shells: 77
Number of basis functions: 231
Charge : -1
Multiplicity: 1
Parallel Job: 6 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-2203.111794	0.029160	0.207350
2	-2203.121323	0.007854	0.073403

3	-2203.122114	0.004405	0.060628
4	-2203.122190	0.002324	0.065443
5	-2203.122235	0.003219	0.035607
6	-2203.122330	0.001174	0.023215
7	-2203.122345	0.001176	0.022787
8	-2203.122371	0.000403	0.012354
9	-2203.122377	0.000366	0.016897
10	-2203.122382	0.000281	0.005364
11	-2203.122384	0.000446	0.005844
12	-2203.122387	0.000573	0.003879
13	-2203.122388	0.000455	0.002180
14	-2203.122389	0.000250	0.000988

Reason for exit: Successful completion
Quantum Calculation CPU Time : 13:04.53
Quantum Calculation Wall Time: 20:00.13
MacSPARTAN '10 Properties Program: (x86/Darwin) build 1.1.0
Reason for exit: Successful completion
Properties CPU Time : .93
Properties Wall Time: .95
molecule M0001 terminated normally
End- molecule "M0001" Fri Jul 12 00:46:29 2013



MacSPARTAN '10 MECHANICS PROGRAM: x86/Darwin 1.1.0
Frequency Calculation
Adjusted 3 (out of 72) low frequency modes
Reason for exit: Successful completion
Mechanics CPU Time : .07
Mechanics Wall Time: .09
MacSPARTAN '10 Quantum Mechanics Program: (x86/Darwin) build 1.1.0v4
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-31G(D)
Number of shells: 77
Number of basis functions: 231
Charge : -1

Multiplicity: 1
Parallel Job: 6 threads
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization
Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-2203.064035	0.008835	0.096218
2	-2203.066386	0.004015	0.139875
3	-2203.066336	0.003346	0.133838
4	-2203.066564	0.002563	0.083128
5	-2203.066723	0.002754	0.033338
6	-2203.066777	0.001862	0.012554
7	-2203.066788	0.001564	0.018828
8	-2203.066798	0.000935	0.017762
9	-2203.066802	0.000390	0.011384
10	-2203.066803	0.000203	0.011268
11	-2203.066805	0.000163	0.014740
12	-2203.066806	0.000179	0.014070
13	-2203.066807	0.000106	0.014745

Reason for exit: Successful completion
Quantum Calculation CPU Time : 11:35.76
Quantum Calculation Wall Time: 18:33.18
MacSPARTAN '10 Properties Program: (x86/Darwin) build 1.1.0
Reason for exit: Successful completion
Properties CPU Time : .97
Properties Wall Time: 1.14
molecule M0001 terminated normally
End- molecule "M0001" Fri Jul 12 00:46:29 2013

12.6) EXPERIMENTAL DETAILS FOR CHAPTER 7

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents are reagents were dried and distilled/recrystallized by standard methods. All ^{19}F NMR spectra were acquired on a Bruker Avance 300 MHz instrument in CD_3CN. The ^{19}F (282 MHz) chemical shifts are given in parts per million (d) with respect to an internal 3-chlorobenzotrifluoride standard (d = -64.2). NMR data are reported in the following format: chemical shift (integration, multiplicity, coupling constants [Hz]). Spectral data were processed with ACD/NMR Processor Academic Edition.[272] Electrochemistry experiments were carried out on a BAS CV-50W potentiostat. UV-Vis spectra were acquired on a Varian Cary-50 spectrophotometer. EPR spectra were acquired on a Bruker EMX spectrometer controlled with a Bruker ER 041 X G microwave bridge operating at X-band (~9.4 GHz), equipped with a liquid helium cryostat. X-ray crystal structures were obtained using a SuperNova diffractometer (equipped with Atlas detector) with Mo *K*α radiation (λ = 0.71073 Å) under the program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). Characterization of *N,N'*-bis(benzylidene)ethane-1,2-diamine,[273] *N,N'*-bis(2,6-dichlorobenzylidene)ethane-1,2-diamine,[2] 3-phenylpropyl-(*S*)-3,3,3-

[272] ACD/NMR Processor Academic Edition, version 12.0, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, **2012**.
[273] Liau, H.; Zhang, H-J.; Wang, S-J.; Mi, A-Q.; Jiang, Y-Z.; Gong, L-Z. *Tetrahedron Lett.* **2005**, *16*, 2901-2907.

trifluoro-2-methoxy-2-phenylpropanoate, [274] benzylcyclopropane, [275] norcarane,[4] 2-phenylbenzylcyclopropane,[276] 3-phenylpropyl-3,3-d_2 acetate,[277] (1*E*,1'*E*)-*N,N'*-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(1-(2,6-dichlorophenyl)methanimine), [278] 3-fluoro-3-phenylpropyl acetate, [279] fluorocyclododecane, [280] fluorocyclohexane,[9] fluorocyclodecane,[9] fluoroadamantane,[9] and n-fluoro-1-hexyl acetate isomers[9] were consistent with literature precedent.

Simplified sp^3 C-H fluorination procedure:

Selectfluor (390 mg, 1.1 mmol), cuprous iodide (10 mg, 0.05 mmol), *N*,*N*'-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. Degassed (with N_2) acetonitrile (6 mL) was added to the reaction flask, and the solution was stirred vigorously at room temperature. After 15 minutes, starting material (0.50 mmol) was added to the reaction flask, and the reaction stirred overnight. Products (previously characterized) were determined by ^{19}F NMR. Product yields were also determined by ^{19}F NMR, upon making a sample tube composed of a 0.3 mL aliquot from the reaction flask and 0.2 mL of a solution of 3-chlorobenzotrifluoride

[274] Neises, B.; Steglich, W. *Angew. Chem. Int. Ed.* **1978**, *17*, 522–524.
[275] Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959,** *81*, 4256-4264.
[276] Aguila, M. J. B.; Badiei, Y. M.; Warren, T. H. *J. Am. Chem. Soc.* **2013,** *135*, 9399-9406.
[277] Kurita, T.; Hattori, K.; Seki, S.; Mizumoto, T.; Aoki, F.; Yamada, Y.; Ikawa, K.; Maegawa, T.; Monguchi, Y; Sajiki, H. *Chem. Eur. J.* **2008**, *14*, 664-673.
[278] Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326-5327.
[279] Lectka, T.; Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G. *Org. Lett.* **2013**, *15*, 1722-1724.
[280] Lectka, T.; Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E. *Angew. Chem. Int. Ed.* **2012**, *42*, 10732-10735.

(internal standard) dissolved in CD_3CN. Note that non-volatile products can typically be isolated by diluting the reaction mixture with Et_2O, filtering through Celite, extracting into Et_2O, drying with $MgSO_4$, filtering, concentrating, and carefully columning on florisil with a non-polar solvent.

Gram-scale synthesis of 1-fluorocyclododecane:

Selectfluor (4.676 g, 13.2 mmol), cuprous iodide (114 mg, 0.6 mmol), *N*,*N*'-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (223 mg, 0.6 mmol), potassium carbonate (83 mg, 0.6 mmol), and cyclododecane (1.008 g, 6.0 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. Degassed acetonitrile (72 mL) - better accomplished via several *free-pump-thaw* cycles on a large scale - was added to the reaction flask, and the solution was stirred vigorously at room temperature for 8 h. The desired product – 1-fluorocyclododecane – was obtained in 50% yield, as determined by ^{19}F NMR.

Liquid-phase EPR general procedure:

Selectfluor (390 mg, 1.1 mmol), cuprous iodide (10 mg, 0.05 mmol), *N*,*N*'-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. Degassed (with N_2) acetonitrile (6 mL) was added to the reaction flask, and the solution was stirred

vigorously at room temperature. After 15 minutes, starting material (0.50 mmol) was added to the reaction flask (where specified), the reaction stirred for the specified time, 2,4,6-tri-tert-butyl nitrosobenzene (14 mg, 0.05 mmol) was added to the reaction flask (if/when specified in text), then an aliquot was transferred via syringe (fit with a disposable syringe filter) to an oven-dried quartz flat cell Bruker ER 160FC-Q immediately prior to collecting an EPR spectrum at room temperature. An additional aliquot was taken simultaneously for ^{19}F NMR analysis of product formation.

Solid-state EPR general procedure:

Selectfluor (390 mg, 1.1 mmol), ^{63}CuI (10 mg, 0.05 mmol), ^{15}N-labelled *N*,*N*'-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. Degassed (with N_2) acetonitrile (6 mL) was added to the reaction flask, and the solution was stirred vigorously at room temperature. After 15 minutes, starting material (0.50 mmol) was added to the reaction flask (where specified), the reaction stirred for the specified time, then an aliquot was transferred via syringe to a 4 mm quartz EPR tube under N_2 and immediately submerged in liquid nitrogen for transport to the EPR spectrometer. Unless otherwise stated, solid-state EPR spectra were collected at 4 K using a temperature-controlled liquid helium cryostat. An

additional aliquot was taken concomitantly for ^{19}F NMR analysis of product formation.

Preparation of ^{63}CuI:

^{63}CuI was prepared from ^{63}Cu metal (86.2 mg, 1.4 mmol) and a slight excess of iodine chips (195.2 mg, 0.77 mmol). The reactants were sealed in an evacuated fused-silica tube, and then the reaction vessel was placed in a furnace. The furnace temperature was ramped at 30°C per hour to a final temperature of 325°C, held at 325°C for 24 hours, and then cooled to room temperature. A powder X-ray diffraction pattern of the resulting product was collected using Cu Ka radiation (1.5418 Å) on a Bruker D8 Focus diffractometer with a LynxEye detector, showing ^{63}CuI as the only phase present.

Voltammetry general procedure:

Differential pulse voltammograms were measured using an Epsilon electrochemical analyzer (Bioanalytical Systems, Inc.) for solutions of the copper(I) compounds in 0.1 M $TBAClO_4$ in acetonitrile with an effective scan rate of 20 mV/s (step potential of 4 mV, pulse width of 50 ms, pulse period of 200 ms, pulse amplitude of 50 mV). Solutions were degassed with Ar for 15 minutes immediately prior to acquisition and maintained in an Ar atmosphere at room temperature. The three-electrode setup [platinum disk (working electrode),

platinum wire (counter electrode), Ag/AgCl (sat. KCl(aq)) (reference electrode)] was calibrated versus ferrocene ($Fe^{+/0}$) before and after all measurements.

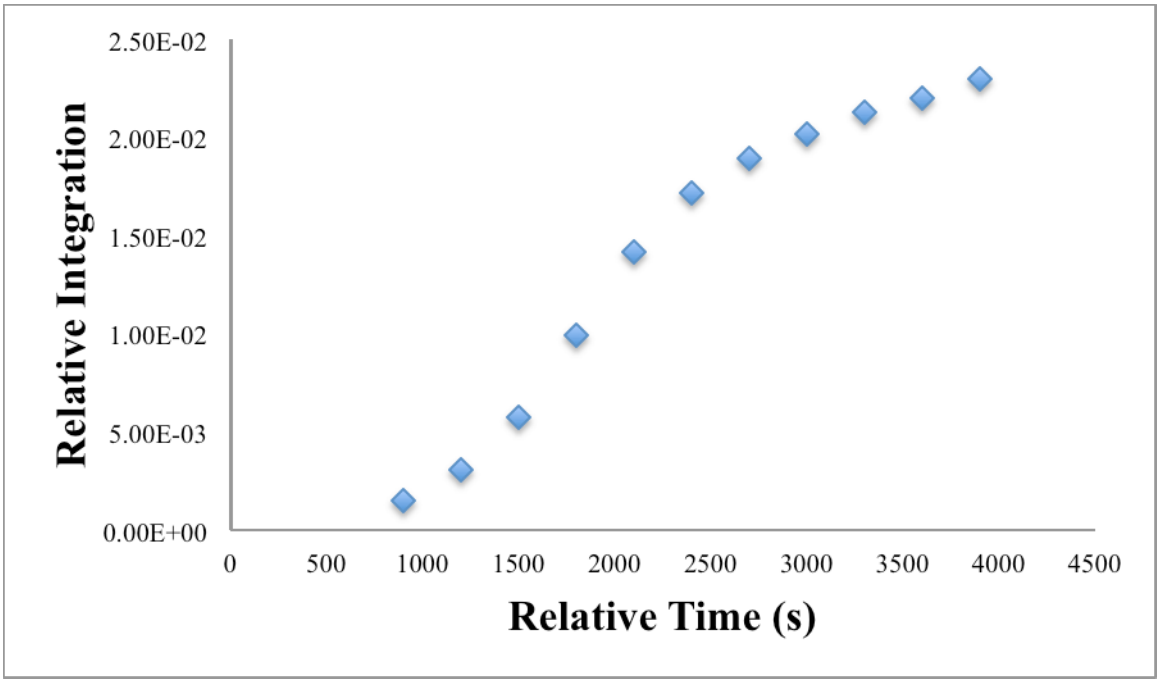
Spectroelectrochemistry procedure:

Spectroelectrochemistry was conducted on a solution of 1-(chloromethyl)-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate in 0.1 M $TBABF_4$ in acetonitrile (degassed with Ar) at room temperature. Controlled potential electrolysis was conducted at +2.5V and +3.0 V (vs. Ag/AgCl) for ~1 h in an Ar atmosphere at room temperature. UV-Vis spectra were acquired periodically on a Varian Cary-50 spectrophotometer.

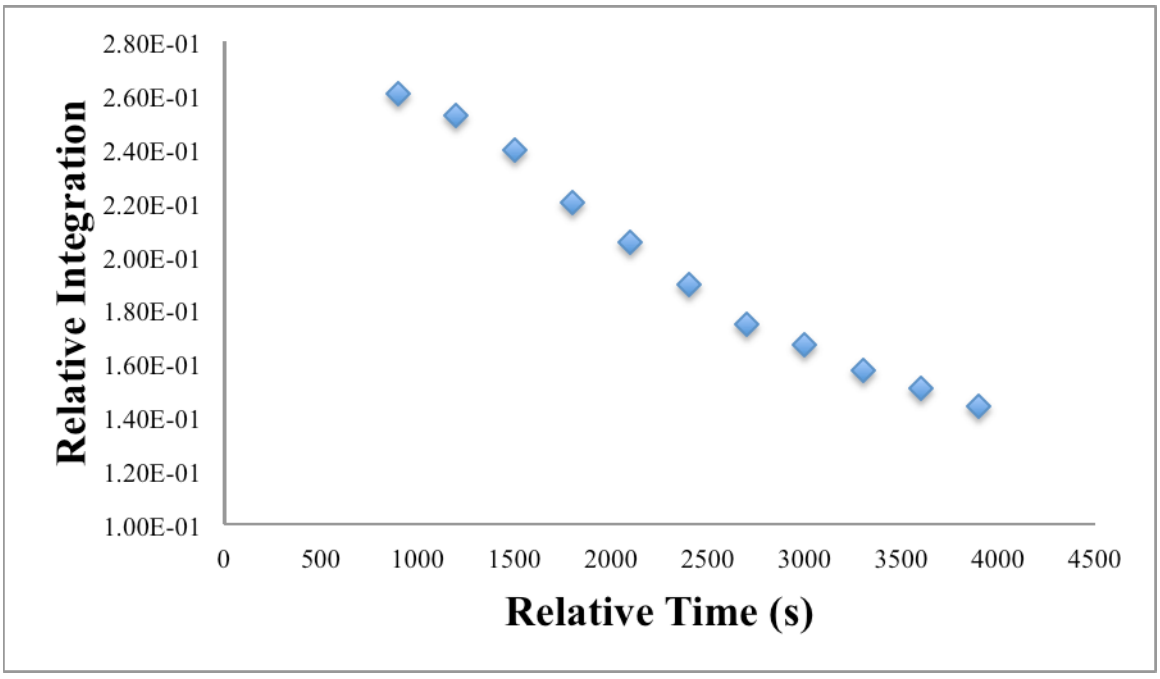
UV-Vis kinetic parameters:

UV-Vis samples were prepared in a flame-dried round bottom flask under N_2, as per the general procedure. The specified solution was passed through a syringe filter after 3 min. of stirring, and the first spectrum was collected at t = 5 min. Up until t = 14.5 min., spectra were collected every 0.5 min. From t = 14.5 min. to t = 20 min., spectra were collected every 1.5 min. From t = 20 min. on, spectra were collected every 5 min. The first 19 spectra are reported in the text.

Complementary loss of Selectfluor N-F signal to increase of F-alkyl signal:

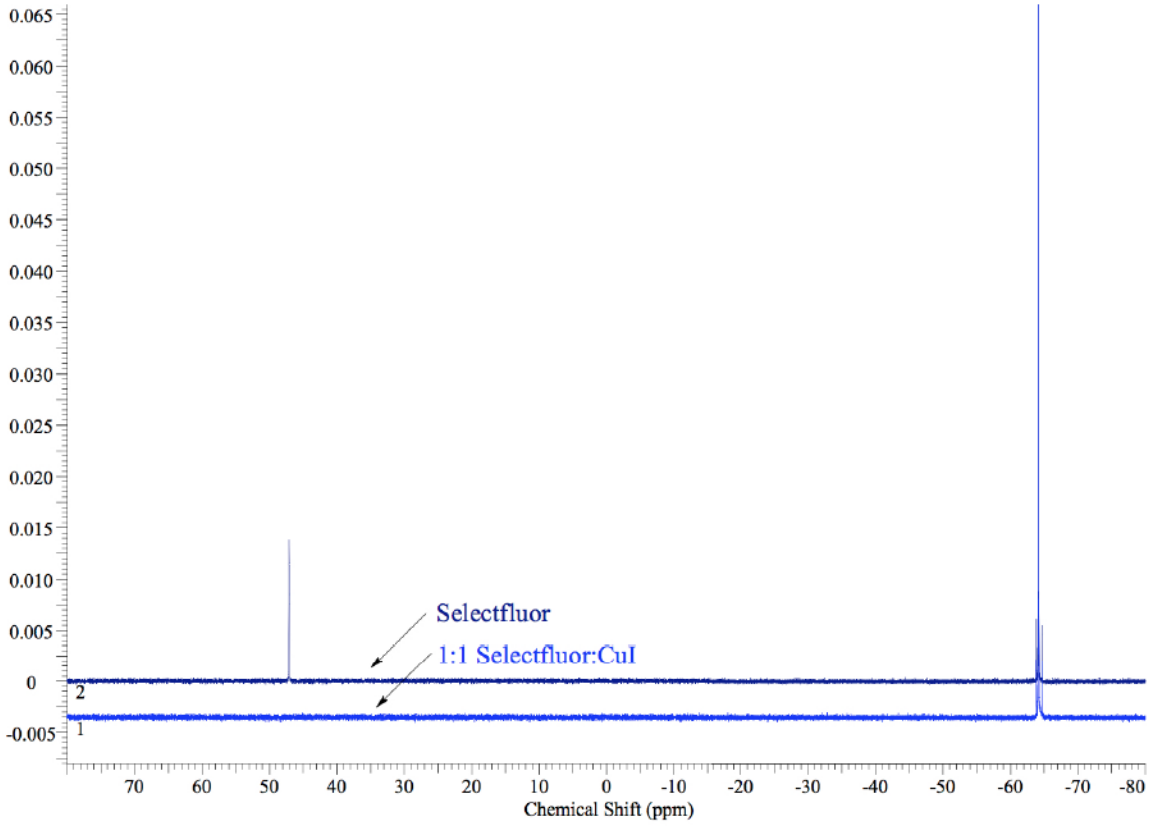


Plot of formation of fluorocyclodecane over time by ^{19}F NMR.



Plot of disappearance of Selectfluor N-F signal over time by ^{19}F NMR.

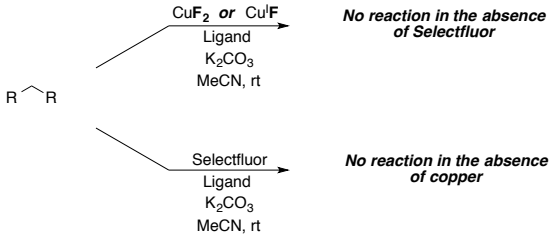
1:1 Selectfluor:CuI ^{19}F NMR



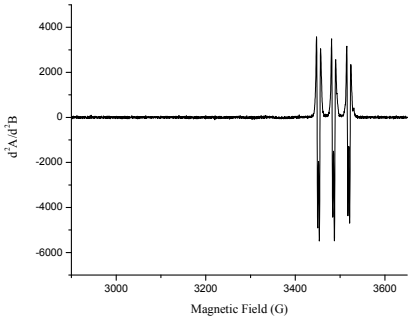
Copper fluoride control experiments:

CuF_2 or $(PPh_3)_3CuF_2$□MeOH (0.50 mmol), *N,N'*-bis(2,6-dichloro-benzylidene)-ethane-1,2-diamine (190 mg, 0.50 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. Degassed (with N_2) acetonitrile (6 mL) was added to the reaction flask, and the solution was stirred vigorously at room temperature. After 15 minutes, starting material (0.50 mmol) was added to the reaction flask, and the reaction stirred overnight. The reaction was conducted with adamantane,

cyclododecane, 3-phenylpropyl acetate, and hexyl acetate with each copper fluoride species, with and without ligand added. In each instance, no fluorinated products were observed without Selectfluor present. Also, no fluorinated products were detected using Selectfluor in the absence of copper.



EPR spectrum of spin-trapped copper



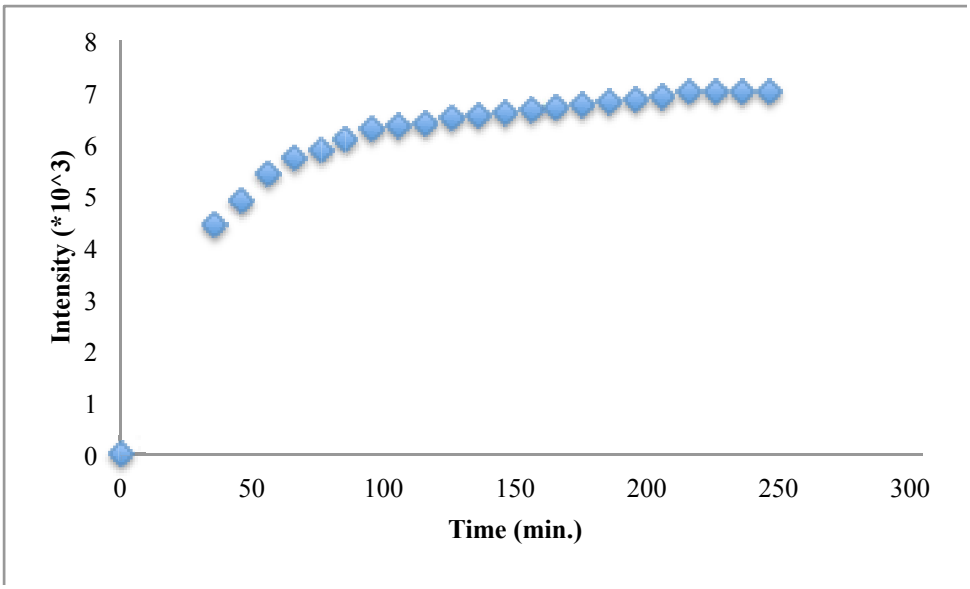
Second derivative graph of spin trapped copper(II) post-induction period.

The presence of two copper(II) species was also confirmed during an attempt to detect and identify any short-lived organic radicals in solution that was made using 2,4,6-tri-*tert*-butyl nitrosobenzene (TTBNB), a known spin trap.[281] As

[281] For an early review on spin trapping reagents and techniques, see: Janzen, E. G. *Acc. Chem. Res.* **1971,** *4*, 31-40.

anticipated, the reagent only trapped copper (regardless of when it was introduced to the reaction), replacing the four-line pattern with a distinct three-line pattern of the nitroso radical. In the second derivative graph, two minima were detected, corresponding to two inflection points in the first derivative graph. A difference of 3.7 G between the two minima is notably greater than previously reported *meta*-proton hyperfine coupling constants, which range from 0.8-1.9 G.[282] Thus, this is less likely observed "splitting" as it is the trapping of two copper(II) species, which is consistent with the solid-state EPR conclusions.

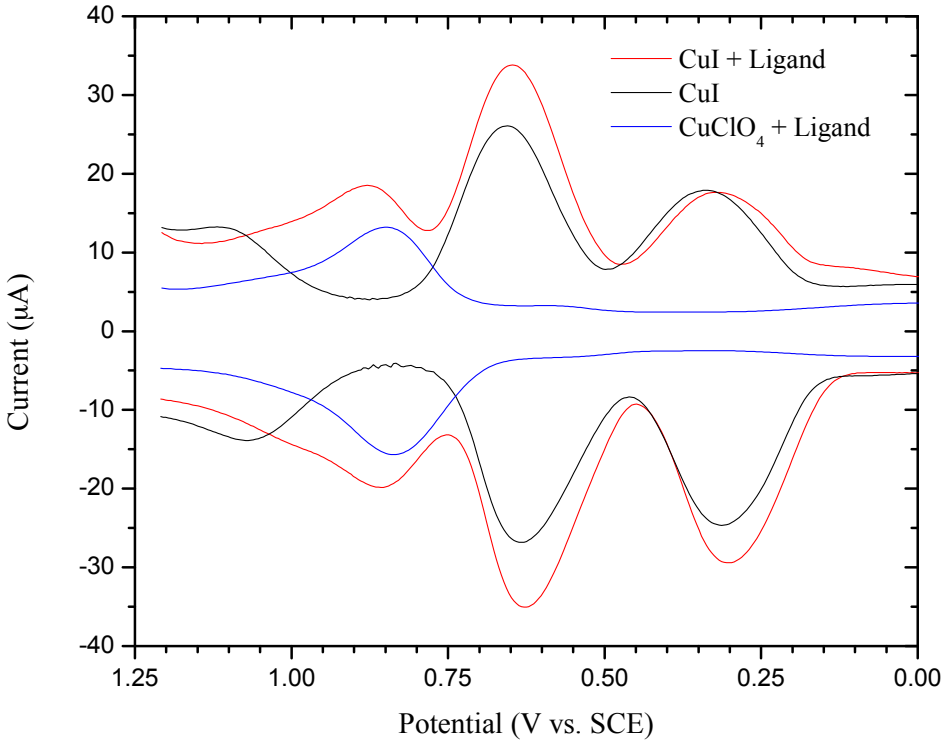
Evolution of copper(II) by EPR over time



Plot of intensity vs. time of a standard reaction in a flat-cell monitored at room temperature by EPR.

[282] Huczynski, A.; Rutkowski, J.; Brzezinski, B. *Struct. Chem.* **2011,** *22*, 627-634.

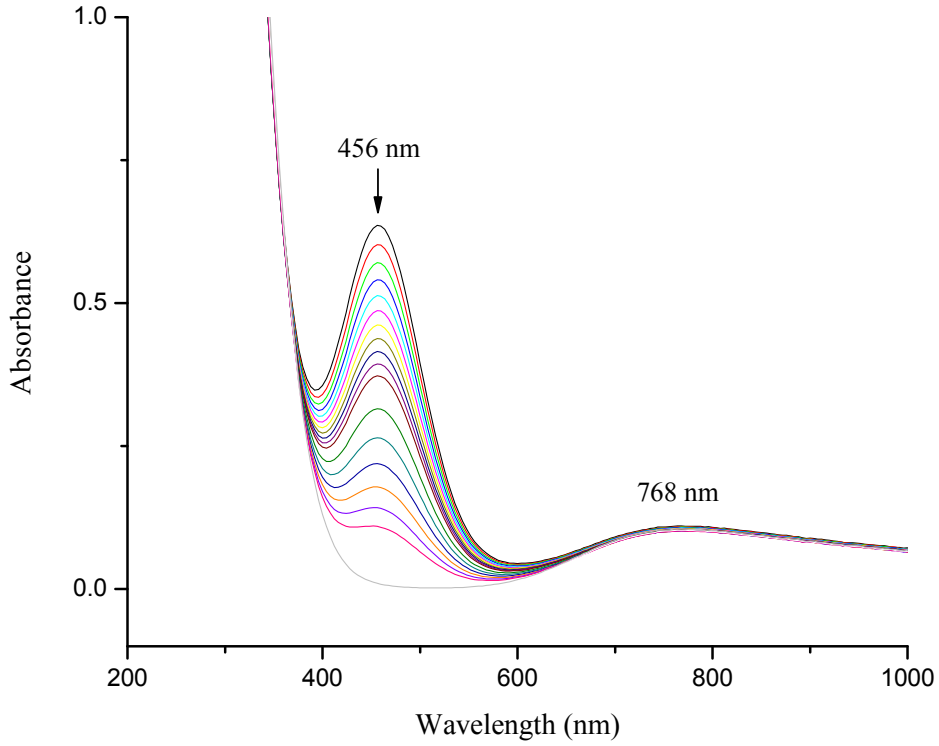
Differential pulse voltammogram control experiments



The differential pulse voltammogram of a 1:1 mixture of cuprous iodide to the *N*,*N*'-bis(2,6-dichlorobenzylidene)ethane-1,2-diamine ligand in 0.1 M tetrabutylammonium perchlorate (TBAP) acetonitrile revealed three quasi-reversible transitions. An additional voltammogram of cuprous iodide and a 1:1 mixture of tetrakis(acetonitrile)copper(I) perchlorate to ligand proved amenable in assigning these waves more accurately. The DPV of cuprous iodide accounted for the two waves at +0.64 V and +0.31 V vs. SCE, which can be respectively

assigned as copper(II/I) and I_2/I^- couples.[283] The DPV of 1:1 tetrakis(acetonitrile)copper(I) perchlorate to ligand mixture matched up with the third $1e^-$ process at a higher oxidation potential of +0.87 V, a slightly tuned copper(II/I) transition. This suggests that our copper species is more easily oxidized in the presence of the ligand.

UV-Vis spectra of CuI and Selectfluor



[283] For iodide redox processes, see: (a) Oskam, G.; Bergeron, B. V.; Meyer, G. J.; Searson, P. C. *J. Phys. Chem. B* **2001,** *105*, 6867-6873. (b) Datta, J.; Bhattacharya, A.; Kundu, K. K. *Bull. Chem. Soc. Jpn.* **1988,** *61*, 1735-1742. (c) Macagno, V. A.; Giordano, M. C.; Arvia, A. J. *Electrochim. Acta* **1969,** *14*, 335-337.

We observe visible bands at 456 nm and 768 nm upon the addition of cuprous iodide to Selectfluor in MeCN under N_2. The broad band at 768 nm is conceivably a new copper(II) absorbance, consistent with our EPR findings. The decreasing absorbance at 456 nm completely replaces the band observed from cuprous iodide alone in MeCN at 424 nm[284] and was later determined to result from an interaction between iodide and Selectfluor. This absorbance was duplicated when taking a UV-Vis spectrum upon mixing Selectfluor with tetrabutylammonium iodide (the interaction between iodide and Selectfluor alone will not effect the fluorination reaction – copper is necessary).

Discussion of copper removal/sequestration experiments

Additional efforts were made to probe the role of copper as either an initiator or a catalyst by attempting to remove or sequester copper during the course of the reaction. First, we considered using a solid-supported copper(I) species in place of cuprous iodide – a silica or resin bound reagent can be filtered out of the reaction (under N_2) at any time. Silica- and resin-supported pyridylmethanimine copper(I) catalysts[285] were suitable replacements for cuprous iodide in effecting the fluorination reaction, and we found that the reaction did proceed in both

[284] Prakash, T. *Adv. Matt. Lett.* **2011,** *2*, 131-135.
[285] Pyridylmethanimine copper(I) catalysts were synthesized according to literature procedure from both amine functionalized silica gel and amino functional cross-linked poly(styrene) beads, pyridine-2-carbaldehyde, and cuprous chloride. See: (a) Clark, A. J.; Filik, R. P.; Haddleton, D. M.; Radigue, A.; Sanders, C. J.; Thomas, G. H.; Smith, M. E. *J. Org. Chem.* **1999,** *64*, 8954-8957. (b) Haddleton, D. M.; Kukulj, D.; Radigue, A. P. *Chem. Commun.* **1999,** 99-100.

instances upon filtering off the solid-support. However, firm conclusions cannot be drawn from these experiments, as there was visibly some degree of copper leaching.

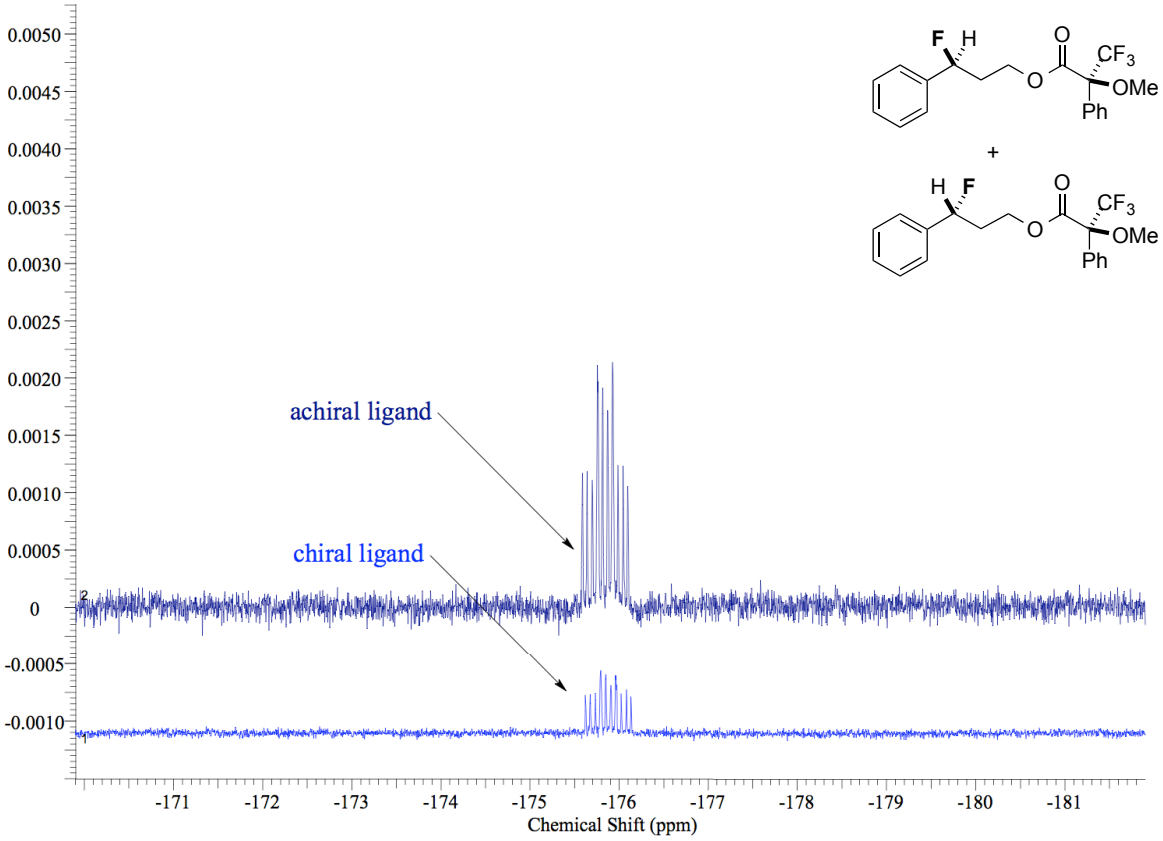
Removing copper from the reaction altogether proved difficult, so we attempted to sequester it using excess ligand. The reaction proceeded with a similar product yield using 0.2 equiv. of ligand (2:1 ligand:copper) from the start of the reaction, as well as when the extra 0.1 equiv. of ligand was introduced after 15 minutes of stirring. Assuming the copper(II) species is bound by both bis(imine) ligands, the atom center would be very hindered.[286] If copper has dynamic redox-activity as a catalyst beyond initiating the reaction, the sequestration using 2:1 ligand:copper during the reaction should slow down the reaction, shut it down altogether, or have an effect on yield, and none of the above seemed to be the case.

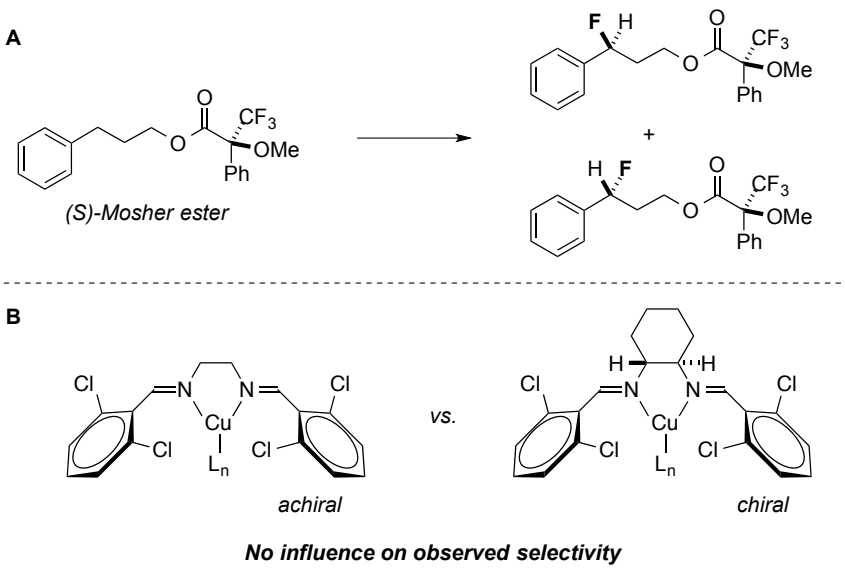
On the other hand, we were able to shut down the reaction immediately using 0.4 equiv. ligand (4 times the amount of copper), that is, by adding 0.3 extra equiv. of ligand any time over the course of the reaction. However, it is very plausible that this is entirely unrelated to the matter of copper sequestration. More likely, the putative radical dication **3** is preferentially oxidizing the bis(imine) ligand instead of the alkane substrate if the imine is present in higher concentrations, which also shuts down the reaction. This is further supported by the fact that the reaction can also be immediately shut down upon addition of 0.1

[286] An attempt was made to grow crystals of the 2:1 bis(imine) ligand:copper species to confirm 2:1 binding, but only the aforementioned polymeric structure crystallized.

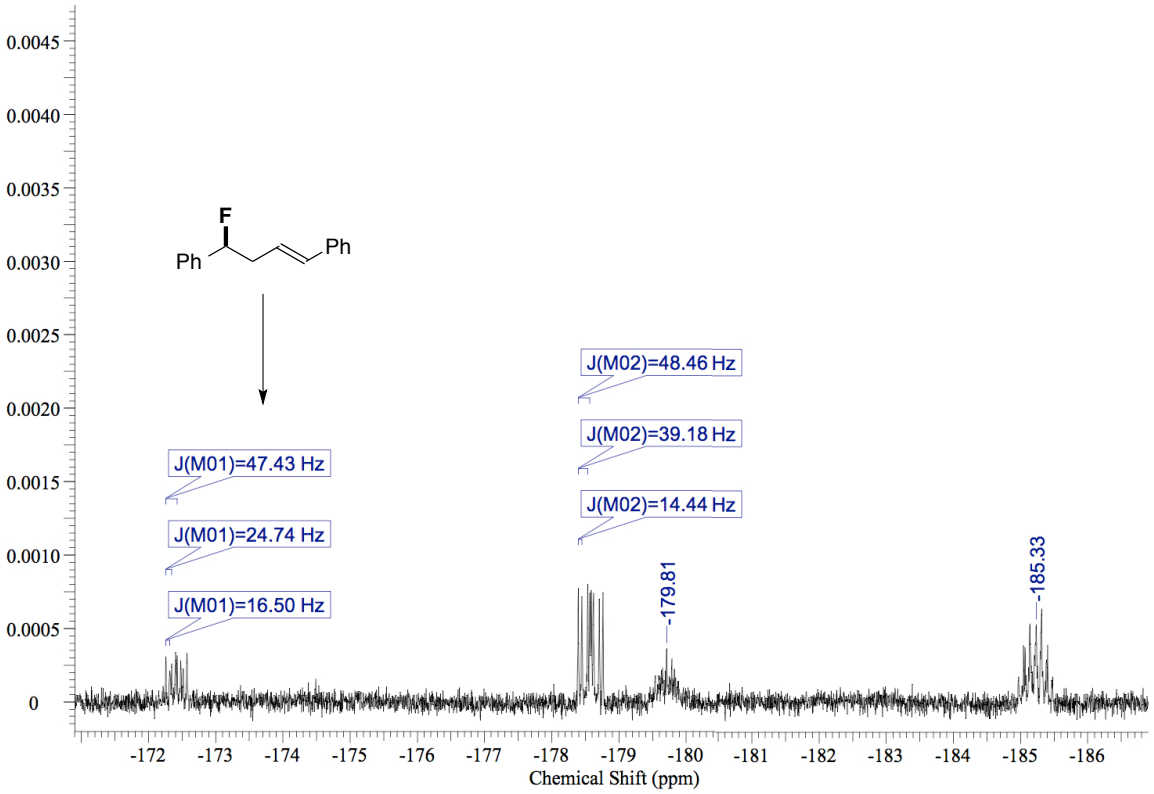
equiv. of tertiary amines, e.g. triethylamine or Hünig's base, that are certainly more easily oxidized than an alkane.

Mosher ester experiment

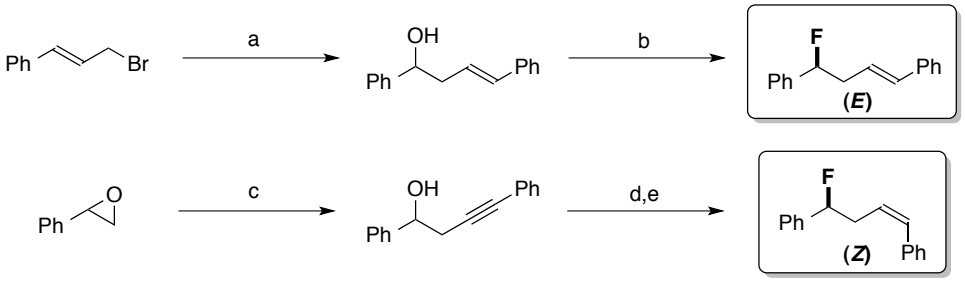




Radical clock rearrangement: 2-phenylbenzylcyclopropane fluorination



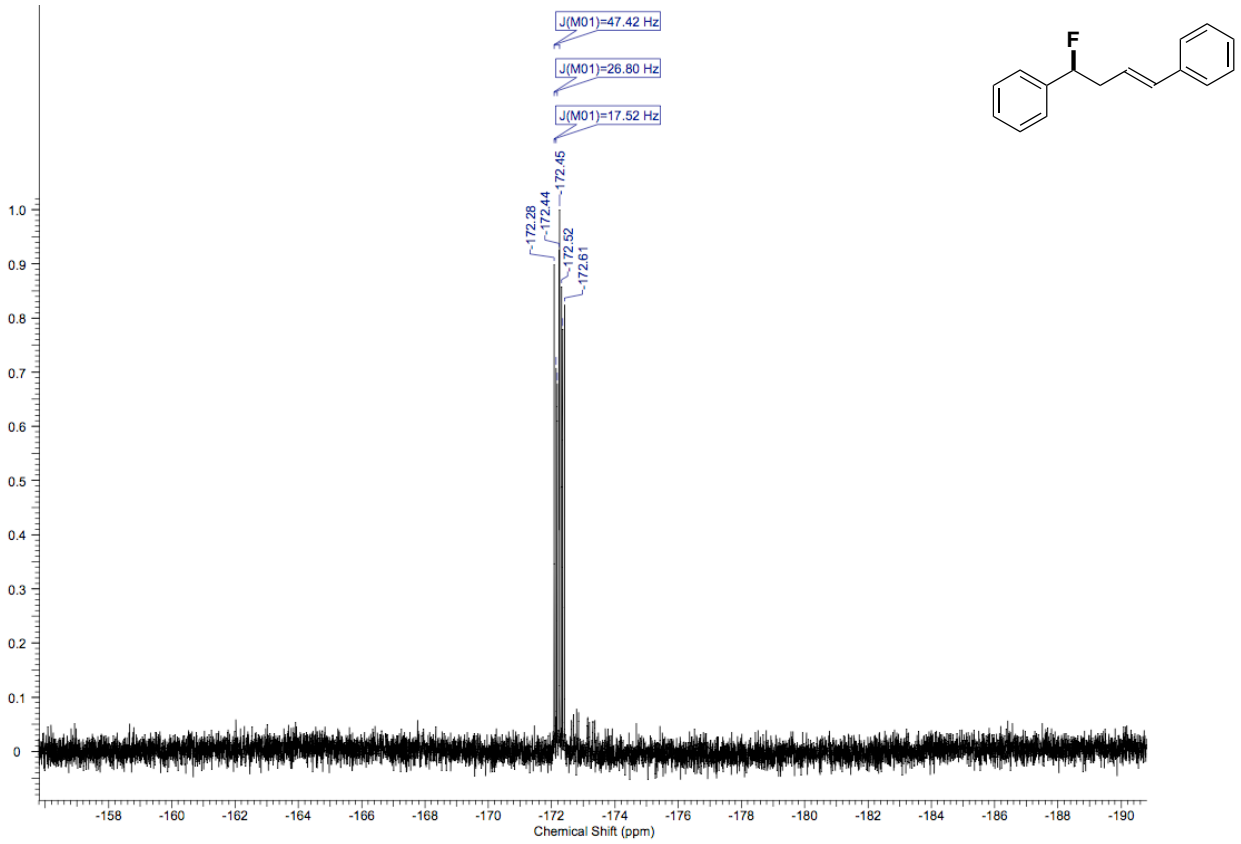
Syntheses of (4-fluorobut-1-ene-1,4-diyl)dibenzene isomers



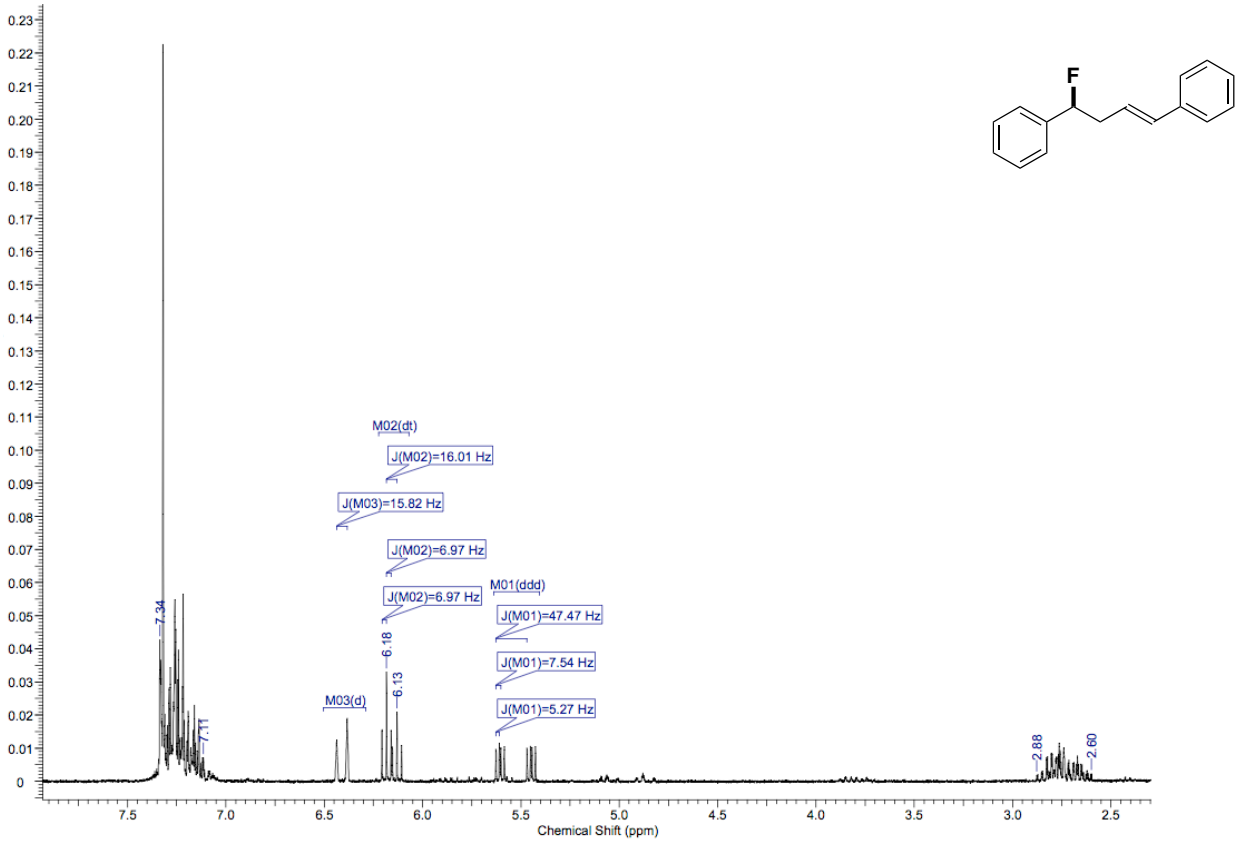
a) PhCOH, Sn, H_2O, rt, 4 days;[287] b) DAST, CH_2Cl_2, -78°C to rt, 16 h;[288] c) PhCCLi, $LiClO_4$, THF, 0°C, 24 h;[289] d) Lindlar's catalyst, H_2, 1 atm, rt, EtOAc, 2 h;[290] e) DAST, CH_2Cl_2, -78°C to rt, 12 h.[288]

Characterization of (*E*)-(4-fluorobut-1-ene-1,4-diyl)dibenzene

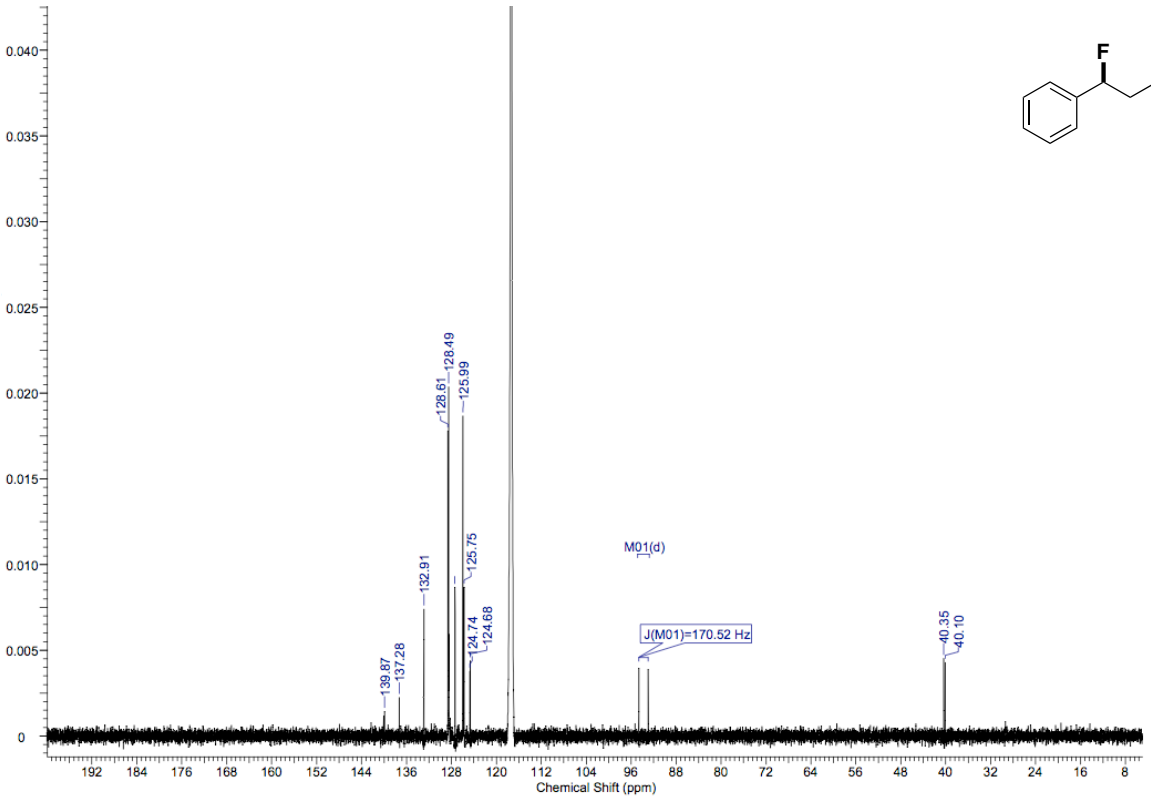
[287] Tan, K-T.; Chng, S-S.; Cheng, H-S.; Loh, T-P. *J. Am. Chem. Soc.* **2003,** *125*, 2958-2963.
[288] Not optimized.
[289] Shindo, M; Sugioka, T.; Shishido, K. *Tetrahedron Lett.* **2004,** *45*, 9265-9268.
[290] Adapted from: Padwa, A.; Rodriguez, A.; Tohidi, M.; Fukunaga, T. *J. Am. Chem. Soc.* **1983,** *105*, 933-943.



^{19}F NMR (CD_3CN): -172.45 (1 F, ddd, J = 47.4, 26.8, 17.5 Hz)

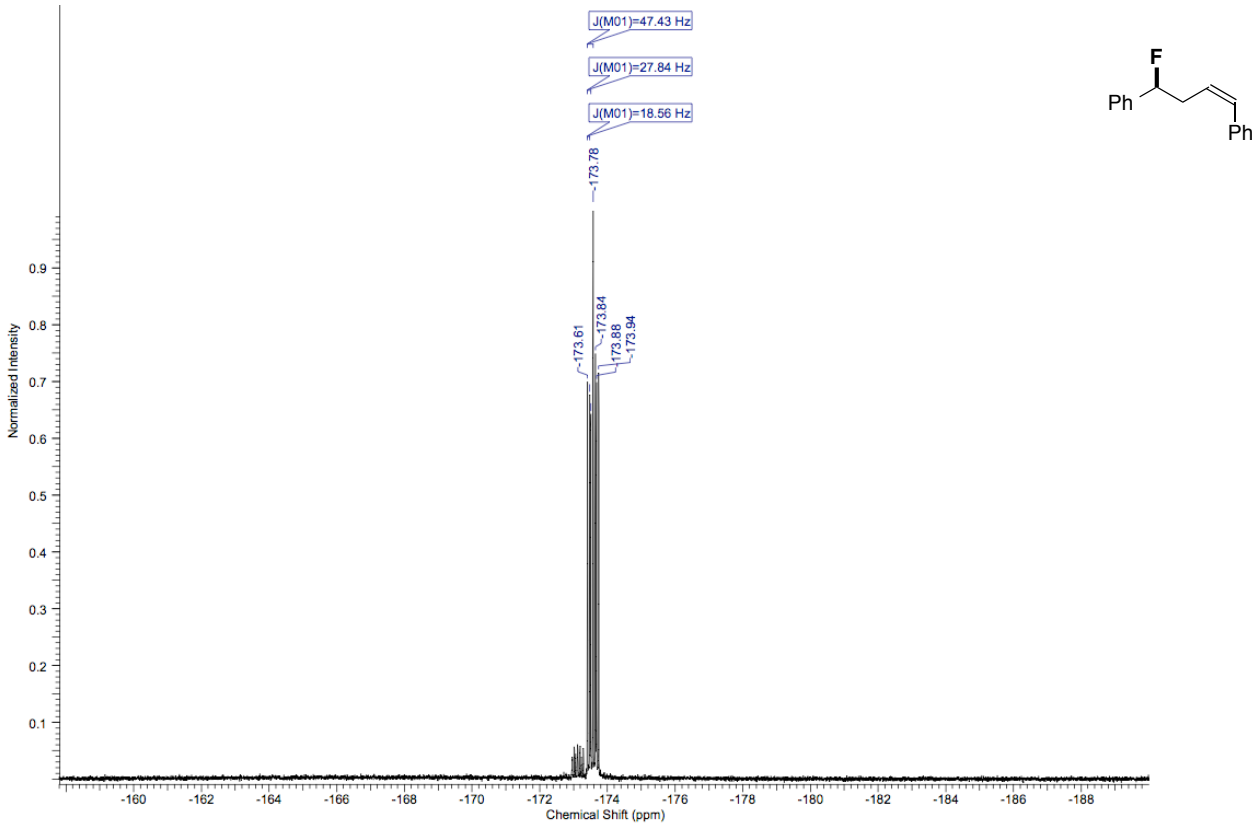


^{1}H NMR (CD_3CN): 7.34-7.11 (10 H, m), 6.41 (1 H, d, J = 15.8 Hz), 6.16 (1 H, dt, J = 16.0, 7.0 Hz), 5.52 (1 H, ddd, J = 47.5, 7.5, 5.3 Hz), 2.88-2.60 (2 H, m).

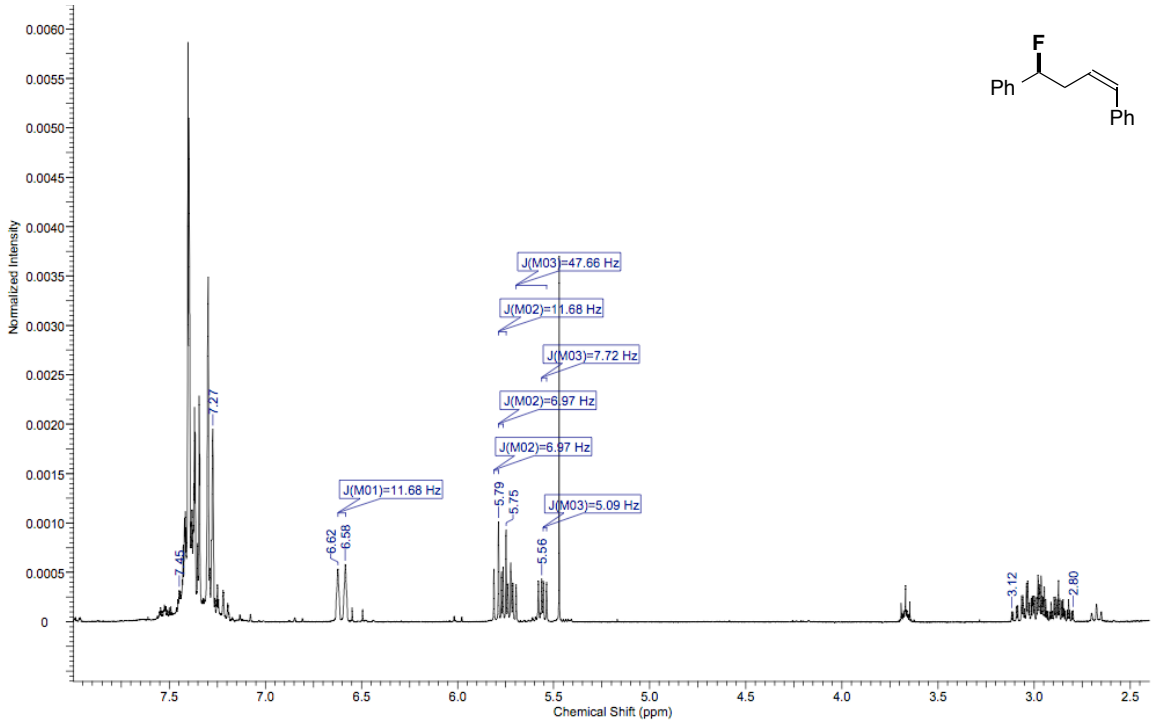


^{13}C NMR (CD_3CN): 139.9, 137.3, 132.9, 128.6, 128.5, 128.4, 128.4, 127.4, 126.0, 125.8, 125.7, 124.7, 124.6, 93.8 (d, J = 170.5 Hz), 40.4, 40.1.

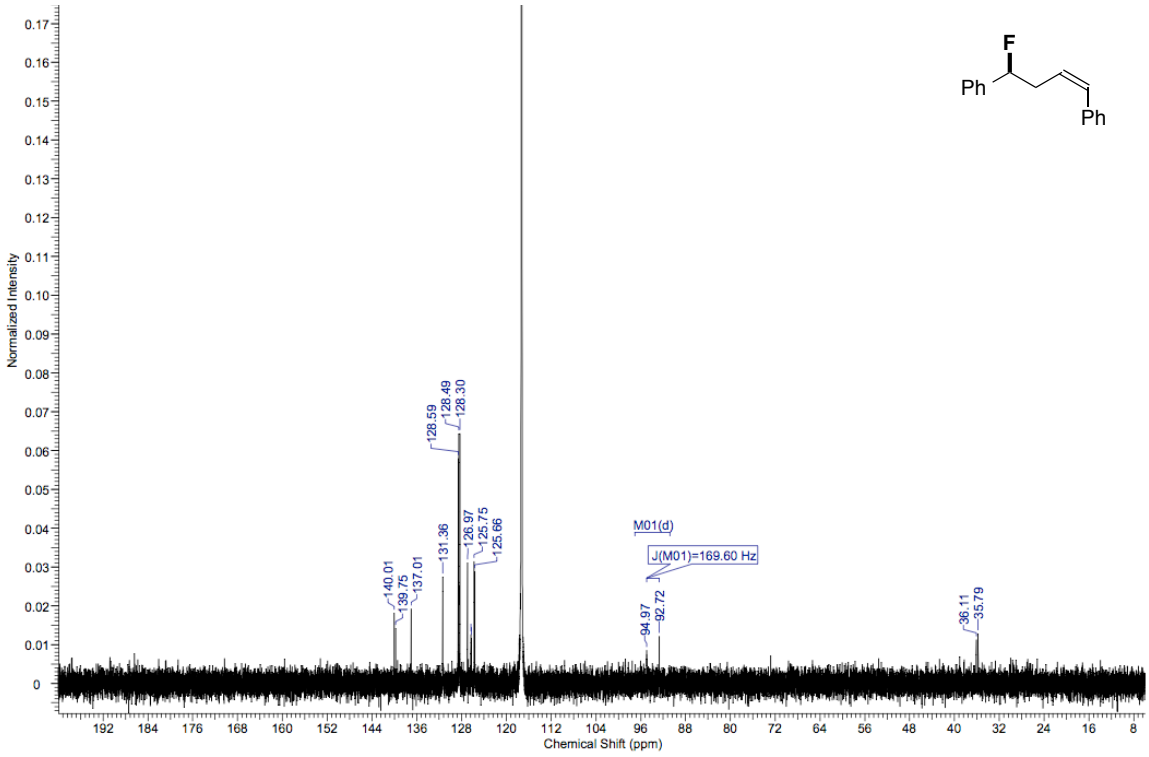
Characterization of (*Z*)-(4-fluorobut-1-ene-1,4-diyl)dibenzene



^{19}F NMR (CD_3CN): -173.78 (1 F, ddd, J = 47.4, 27.8, 18.6 Hz)



^{1}H NMR (CD_3CN): 7.45-7.27 (10 H, m), 6.60 (1 H, d, J = 11.7 Hz), 5.77 (1 H, dt, J = 11.7, 7.0 Hz), 5.64 (1 H, ddd, J = 47.7, 7.7, 5.1 Hz), 3.12-2.80 (2 H, m).



^{13}C NMR (CD_3CN): 140.0, 139.8, 137.0, 131.4, 128.6, 128.5, 128.3, 127.0, 125.8, 125.7, 93.8 (d, J = 169.6Hz), 36.1, 35.8.

Relative *n*-fluoro-hexyl acetate ^{19}F NMR integrations

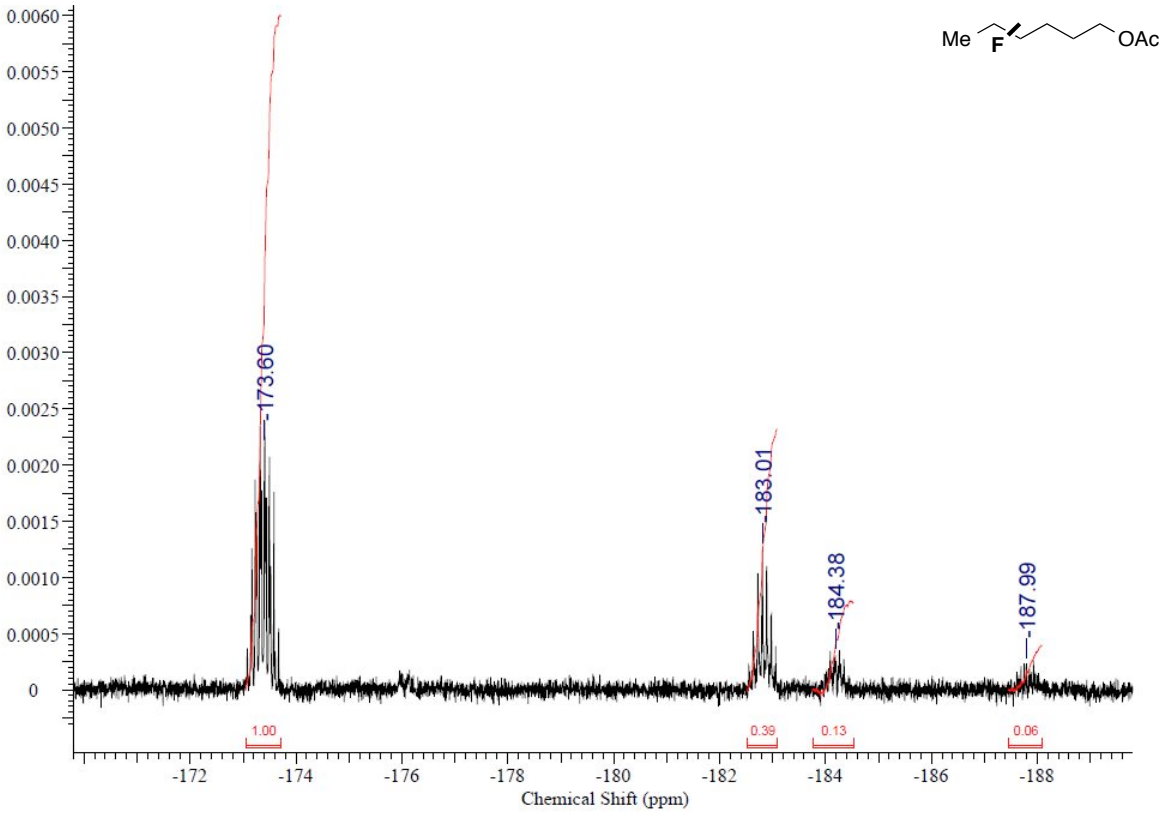


Table of intrinsic hexyl acetate radical stabilities

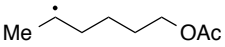
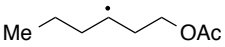
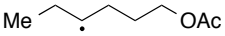
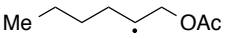
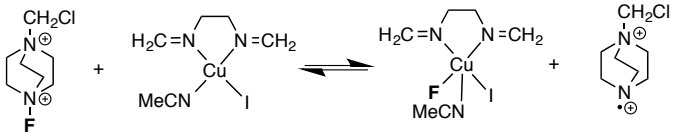
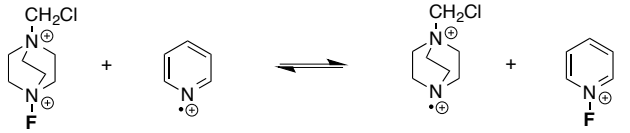
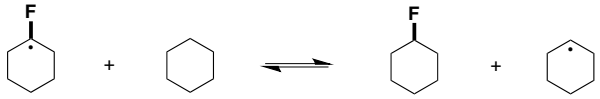
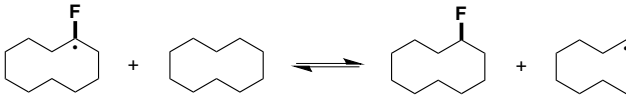
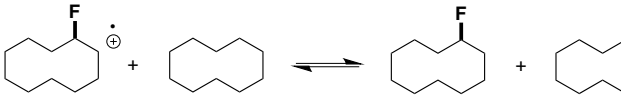
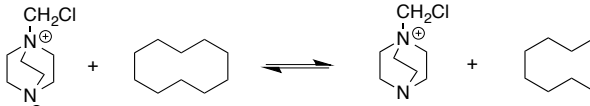
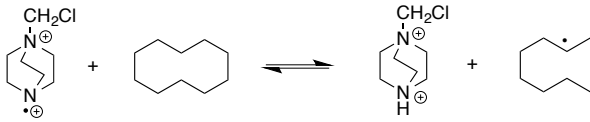
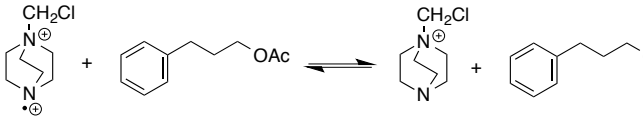
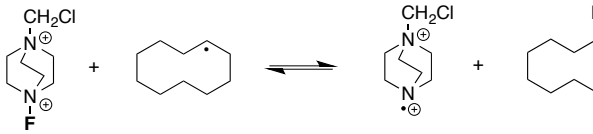
Radical Species	*Relative Selectivity of Product by ^{19}F NMR*	*$E_{relative}$ in kcal/mol B3LYP/6-311++G***	*RI-MP2/6-311++G***
	1.00	0.000	0.000
	0.39	+ 0.117	+ 0.311
	0.14	+ 0.181	+ 0.324
	0.05	+ 1.112	+ 1.529

Table of isodesmic reactions: predictive properties of radical cations

Isodesmic Reaction	*ΔE (kcal/mol)*
	-3.0*
	-14.6**
	0.8
	5.4
	0.2
	-1.5
	18
	-13
	-2.3
	-52
	6.0

All geometry optimizations were performed at B3PW91/6-311+G**(MeCN), unless otherwise stated. *Geometry optimizations performed at B3PW91/DGDZVP(MeCN). **Geometry optimizations performed at B3LYP/6-311++G**(MeCN).

Compiled initial rate data*

Rate (Int./sec)	[3-phenylpropyl acetate]	[Selectfluor]	[CuI-Ligand]	[K2CO3]
1.02E-05	0.083	0.183	0.0083	0.017
7.40E-06	0.057	0.183	0.0083	0.017
4.72E-06	0.042	0.183	0.0083	0.017

Rate (M/sec)	[Cyclodecane]	[Selectfluor]	[CuI-Ligand]	[K2CO3]
7.69E-07	0.083	0.183	0.0083	0.017
5.32E-07	0.062	0.183	0.0083	0.017

Rate (Int./sec)	[3-phenylpropyl acetate]	[Selectfluor]	[CuI-Ligand]	[K2CO3]
4.72E-06	0.042	0.183	0.0083	0.017
3.87E-06	0.042	0.142	0.0083	0.017

Rate (Int./sec)	[3-phenylpropyl acetate]	[Selectfluor]	[CuI-Ligand]	[K2CO3]
1.02E-05	0.083	0.183	0.0083	0.017
9.47E-06	0.083	0.183	0.0042	0.017

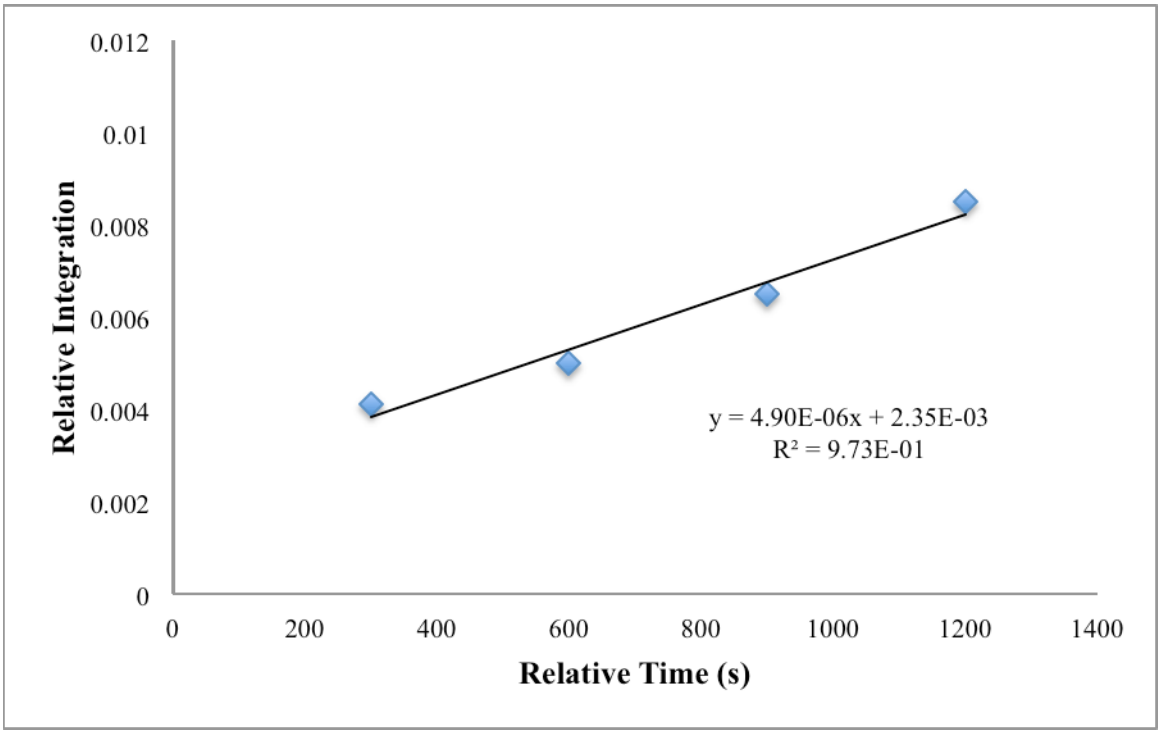
Rate (Int./sec)	[3-phenylpropyl acetate]	[Selectfluor]	[CuI-Ligand]	[K2CO3]
1.09E-05	0.083	0.183	0.0083	0.025
1.02E-05	0.083	0.183	0.0083	0.017

*Reported rates are the average of two runs.

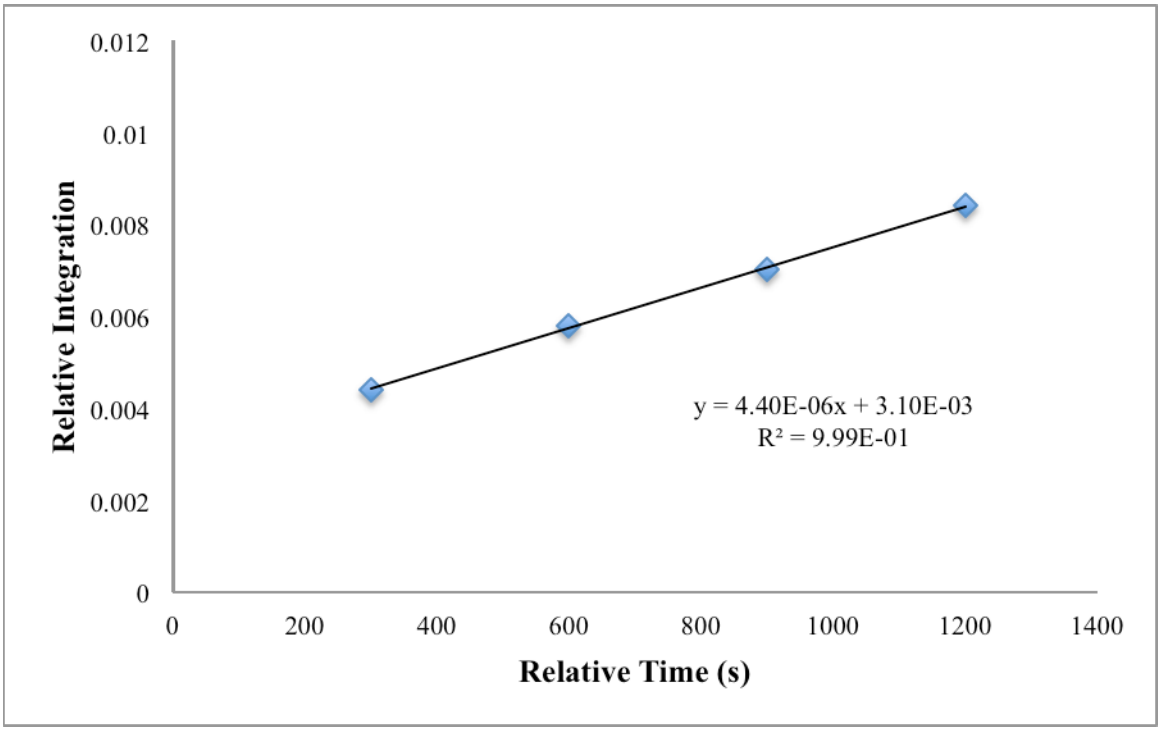
Procedure for rate studies with 3-phenylpropyl acetate:

Selectfluor (390 mg, 1.1 mmol), cuprous iodide (10 mg, 0.05 mmol), *N,N'*-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. A degassed (with N_2) mixture of 4:1 CH_3CN:CD_3CN (6 mL) was added to the reaction flask, and the solution was stirred vigorously at room temperature. After 10 minutes, 3-chlorobenzotrifluoride (0.02 mL, 0.15 mmol) was added via syringe. After 15

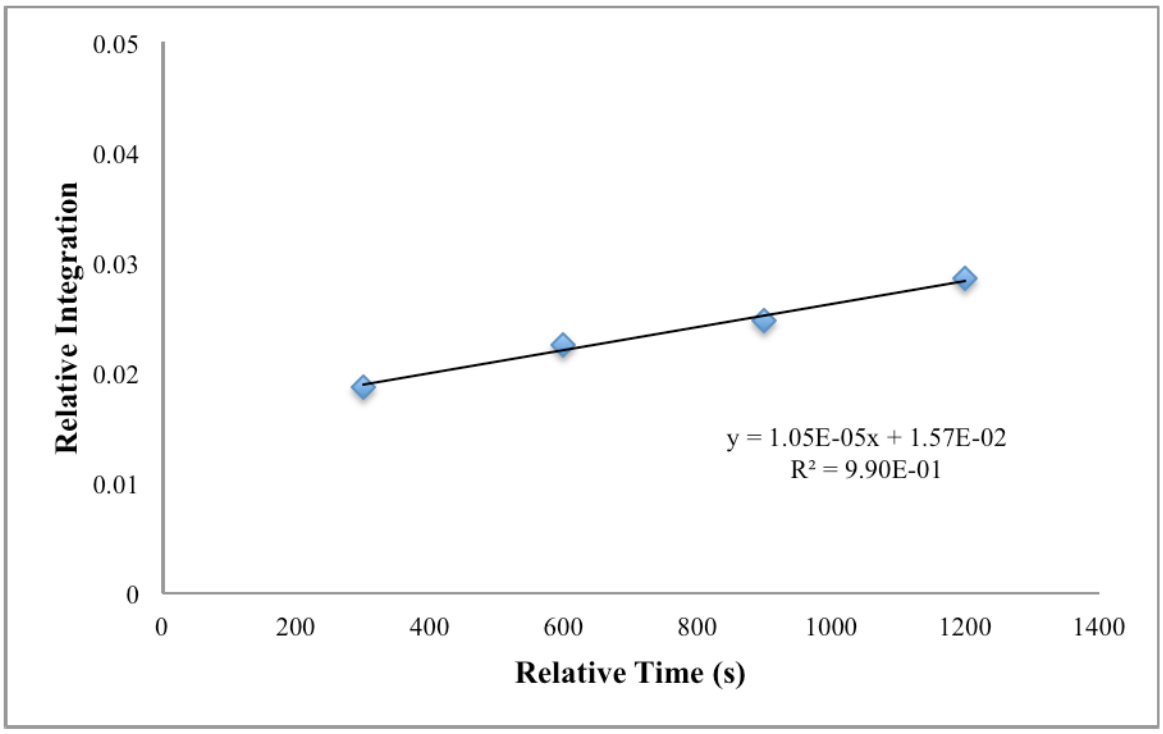
minutes, 3-phenylpropyl acetate (0.09 mL, 0.50 mmol) was added to the reaction flask. The reaction solution stirred for an additional 2 minutes, then 0.5 mL was transferred via syringe from the reaction flask to an NMR tube fit with a septum under N_2. A ^{19}F NMR spectrum of the same sample was collected every 300 seconds at room temperature. Product concentrations were determined using 3-chlorobenzotrifluoride as an internal standard.



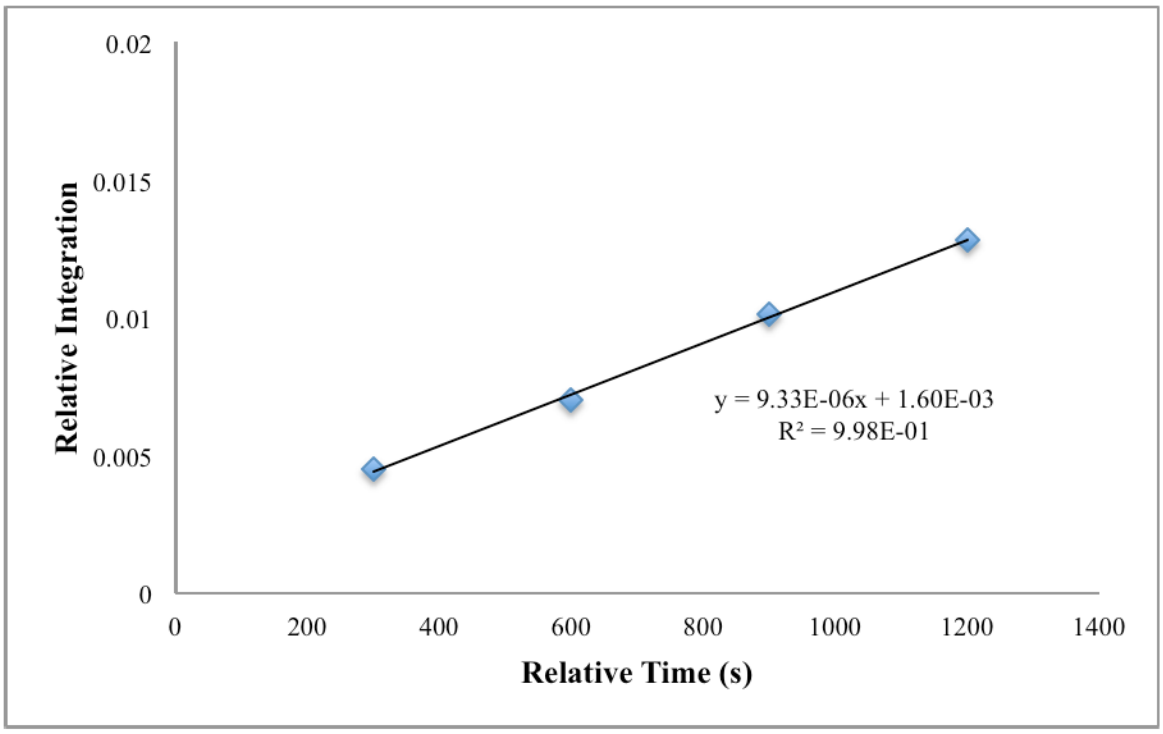
Initial rate of formation of 3-fluoro-3-phenylpropyl acetate starting with [0.183 M] Selectfluor by ^{19}F NMR.



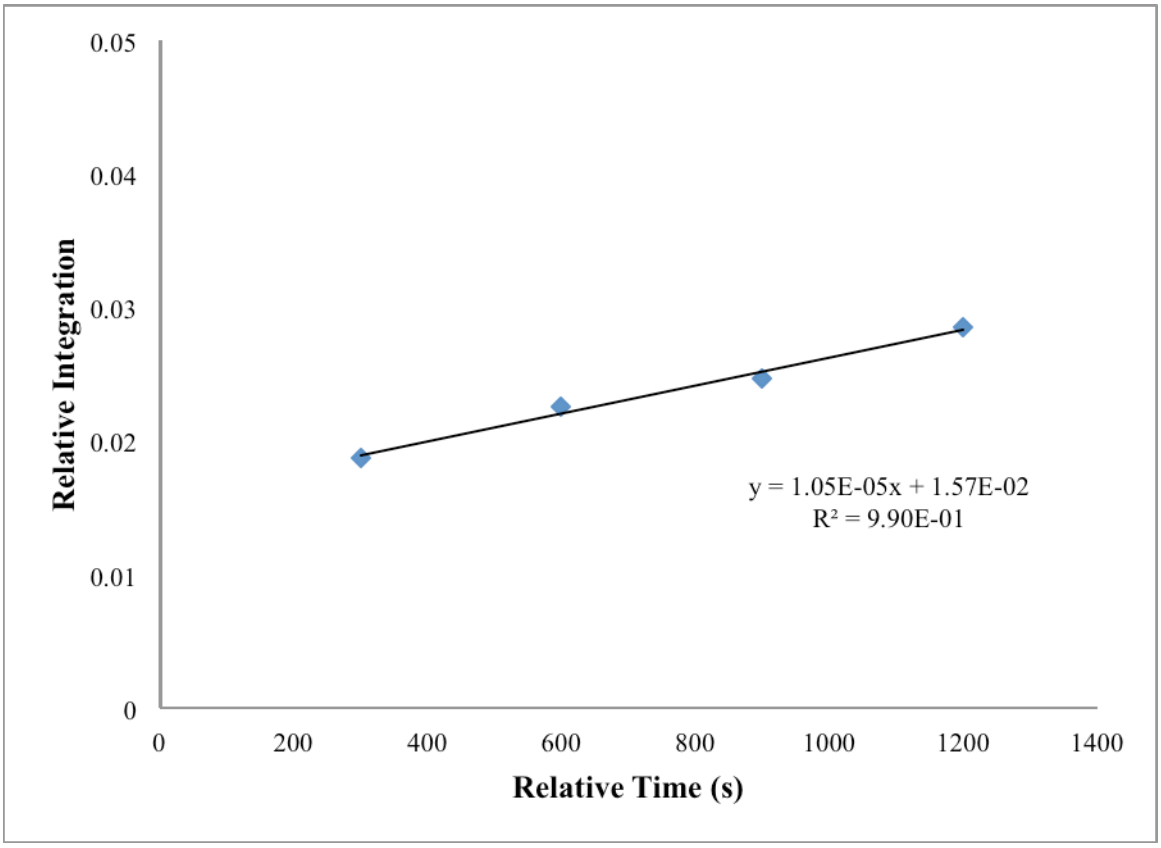
Initial rate of formation of 3-fluoro-3-phenylpropyl acetate starting with [0.142 M] Selectfluor by ^{19}F NMR.



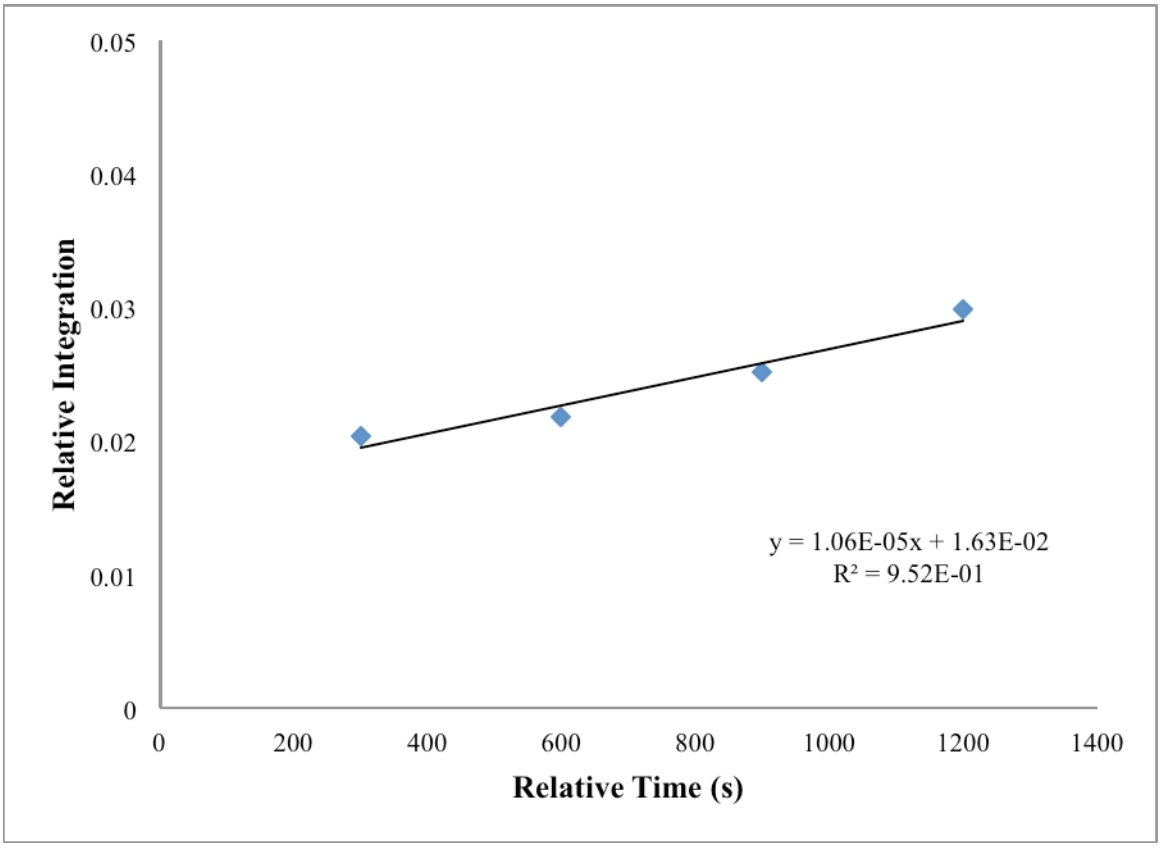
Initial rate of formation of 3-fluoro-3-phenylpropyl acetate starting with [0.0083 M] CuI□bis(imine) ligand by ^{19}F NMR.



Initial rate of formation of 3-fluoro-3-phenylpropyl acetate starting with [0.0042 M] CuI□bis(imine) ligand by ^{19}F NMR.



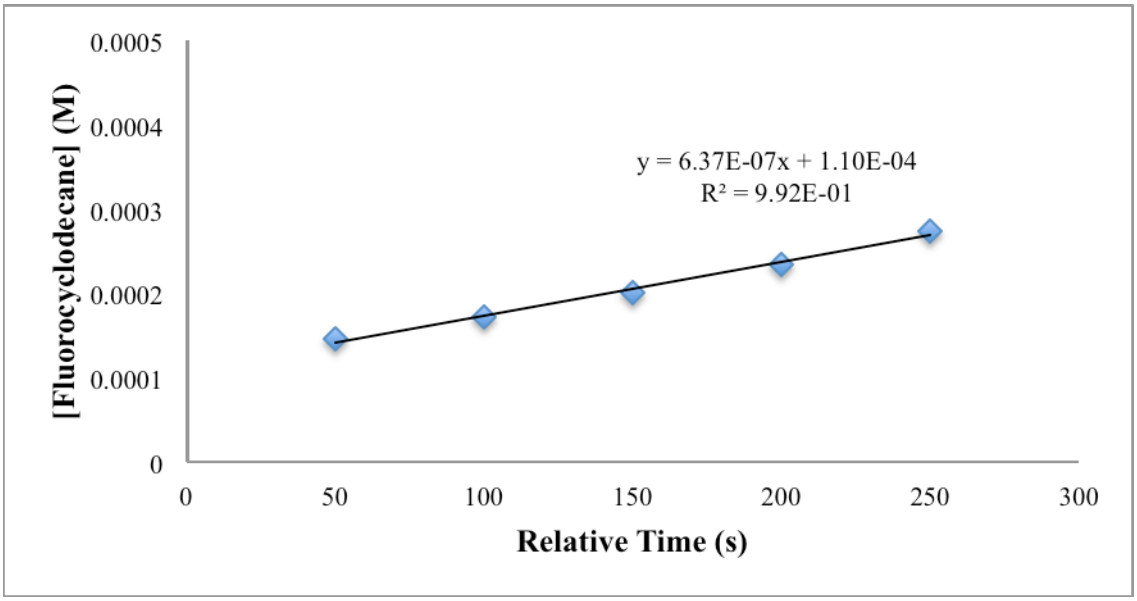
Initial rate of formation of 3-fluoro-3-phenylpropyl acetate starting with [0.017 M] K_2CO_3 by ^{19}F NMR.



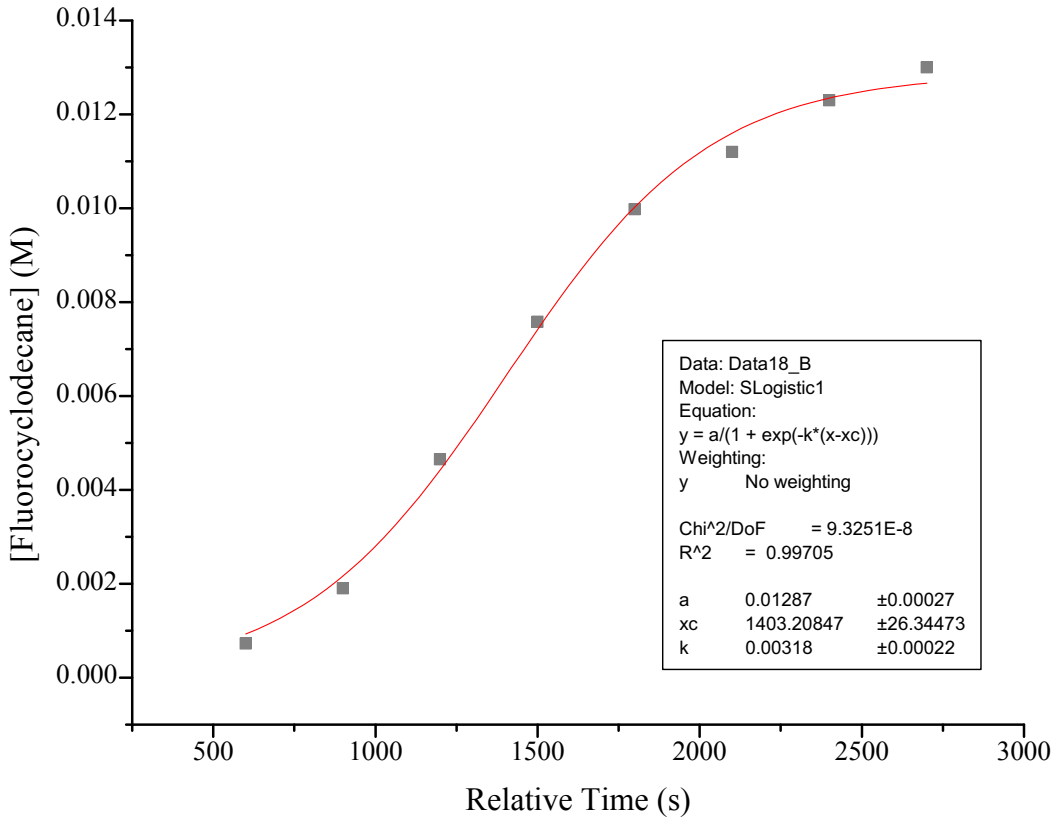
Initial rate of formation of 3-fluoro-3-phenylpropyl acetate starting with [0.025 M] K_2CO_3 by ^{19}F NMR.

Procedure for rate studies with cyclodecane:

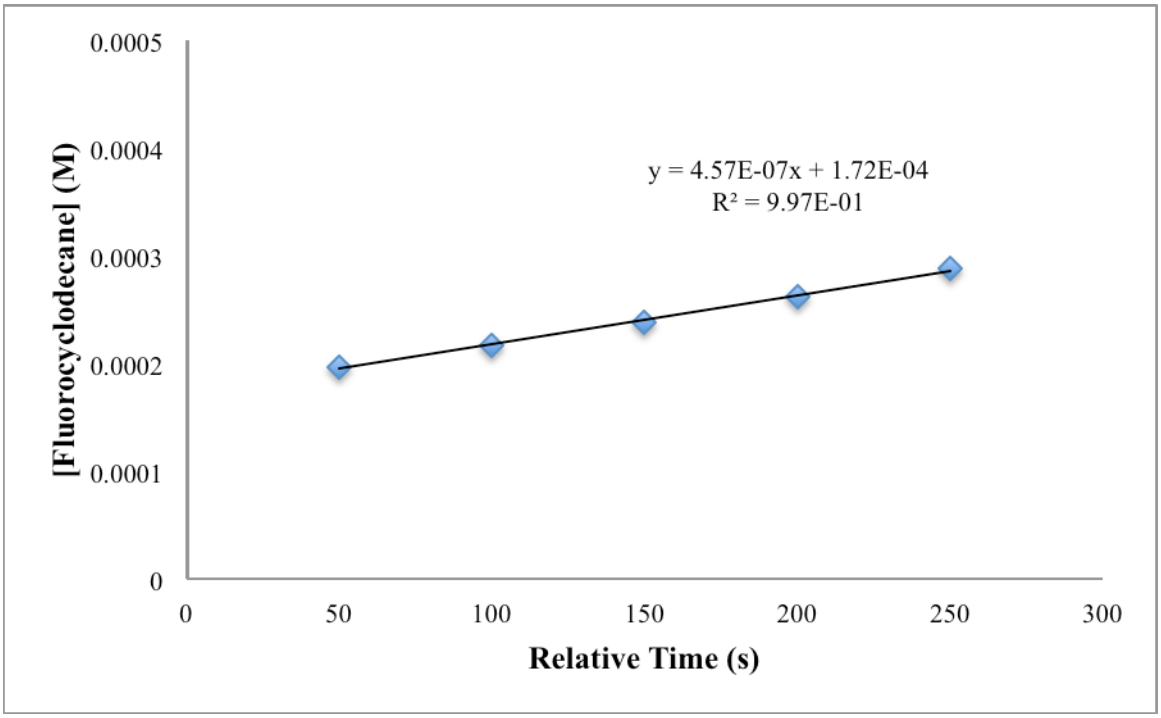
Selectfluor (390 mg, 1.1 mmol), cuprous iodide (10 mg, 0.05 mmol), *N,N'*-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. A degassed (with N_2) mixture of 4:1 CH_3CN:CD_3CN (6 mL) was added to the reaction flask; the solution was immediately cooled to 0°C and stirred vigorously. After 10 minutes, 3-chlorobenzotrifluoride (0.02 mL, 0.15 mmol) was added via syringe. After 15 minutes, cyclodecane (0.08 mL, 0.50 mmol) was added to the reaction flask. The reaction solution stirred for an additional 2 minutes, then 0.5 mL was transferred via syringe from the reaction flask to an NMR tube in an ice bath fit with a septum under N_2. A ^{19}F NMR spectrum of the same sample was collected every 300 seconds at 10°C. Product concentrations were determined using 3-chlorobenzotrifluoride as an internal standard. The data points were fitted to the equation of a sigmoidal curve (seen below) with high coefficients of determination, and this equation was used to extrapolate five points in the initial rate regime (within 600 s of first reported data point, as small peaks were observed 300 s and 600 s prior to the first reported data point, but could not be accurately integrated). All curves were fit/analyzed in the exact same manner.



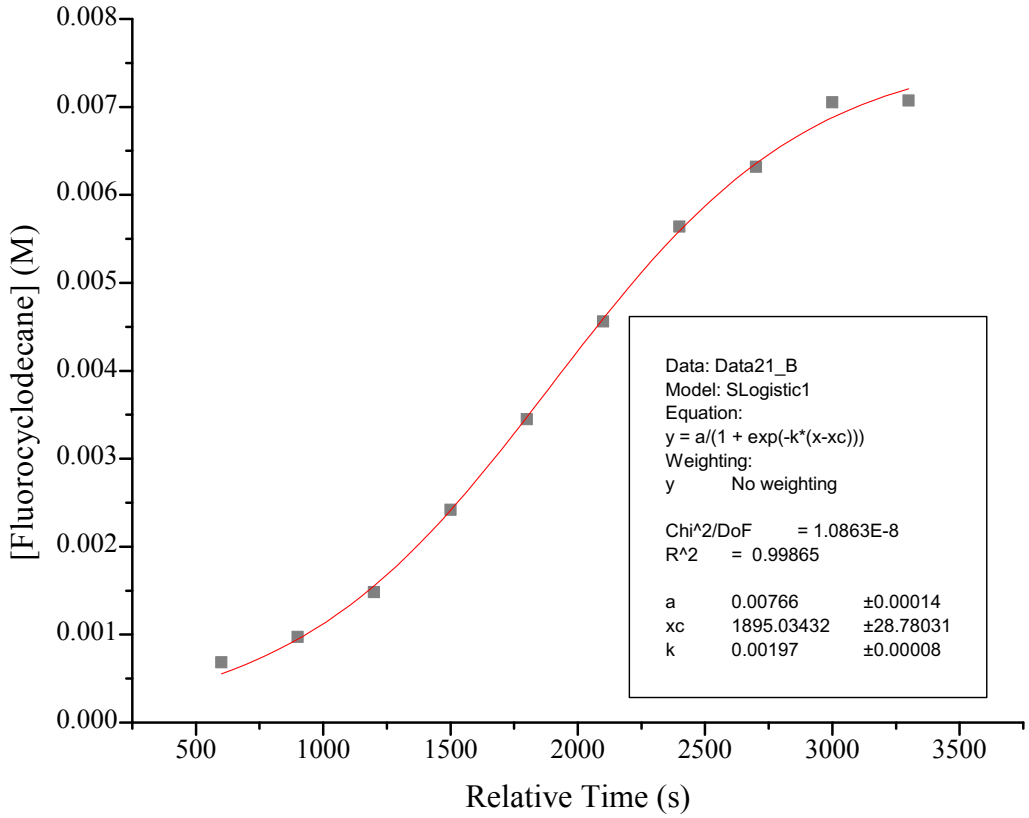
Extrapolated initial rate of formation of fluorocyclodecane starting with [0.083 M] cyclodecane by ^{19}F NMR.



Sigmoidal fit for appearance of fluorocyclodecane starting with [0.083 M] cyclodecane by ^{19}F NMR.



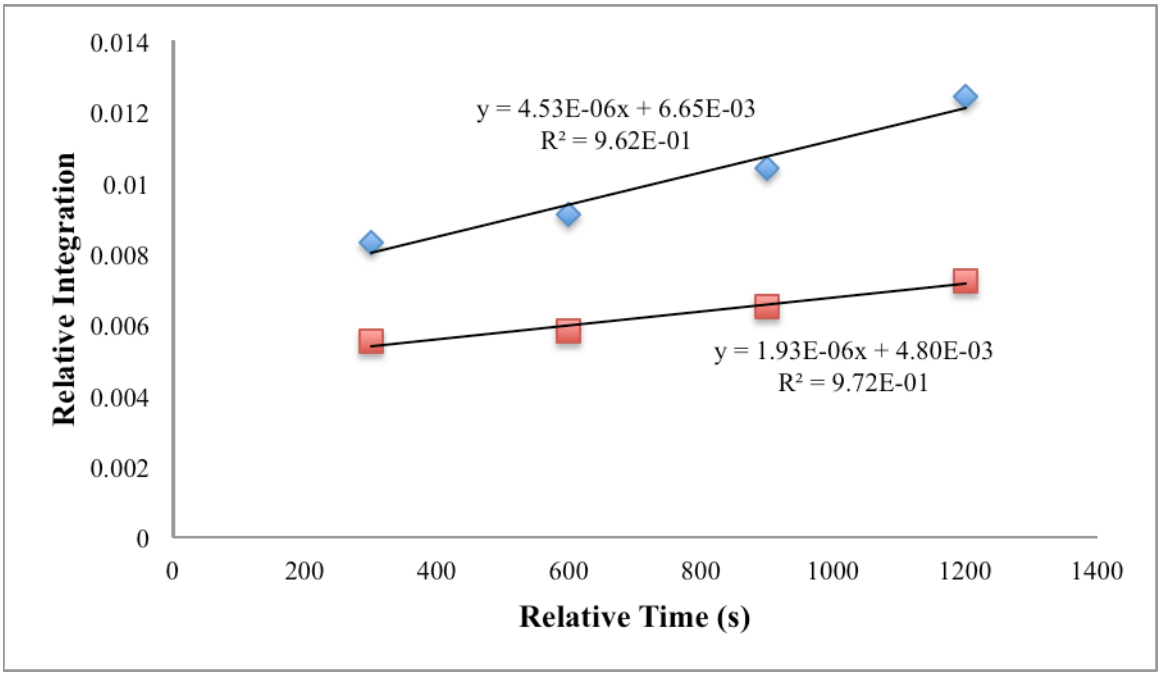
Extrapolated initial rate of formation of fluorocyclodecane starting with [0.062 M] cyclodecane.



Sigmoidal fit for appearance of fluorocyclodecane starting with [0.062 M] cyclodecane by ^{19}F NMR.

Competitive KIE: 3-phenylpropyl acetate

Selectfluor (390 mg, 1.1 mmol), cuprous iodide (10 mg, 0.05 mmol), *N,N'*-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. A degassed (with N_2) mixture of 4:1 CH_3CN:CD_3CN (6 mL) was added to the reaction flask, and the solution was stirred vigorously at room temperature. After 10 minutes, 3-chlorobenzotrifluoride (0.02 mL, 0.15 mmol) was added via syringe. After 15 minutes, a mixture of 3-phenylpropyl acetate, 3-phenylpropyl-3-*d* acetate, and 3-phenylpropyl-3,3-d_2 acetate (0.09 mL, 0.50 mmol) was added to the reaction flask (ca. 50% incorporation of deuterium in the benzylic position by ^{1}H NMR). The reaction solution stirred for an additional 2 minutes, then 0.5 mL was transferred via syringe from the reaction flask to an NMR tube fit with a septum under N_2. A ^{19}F NMR spectrum of the same sample was collected every 300 seconds at room temperature. Product concentrations were determined using 3-chlorobenzotrifluoride as an internal standard. $k_H/k_D \approx 2.3$ (average of two runs: 2.3 + 2.3).

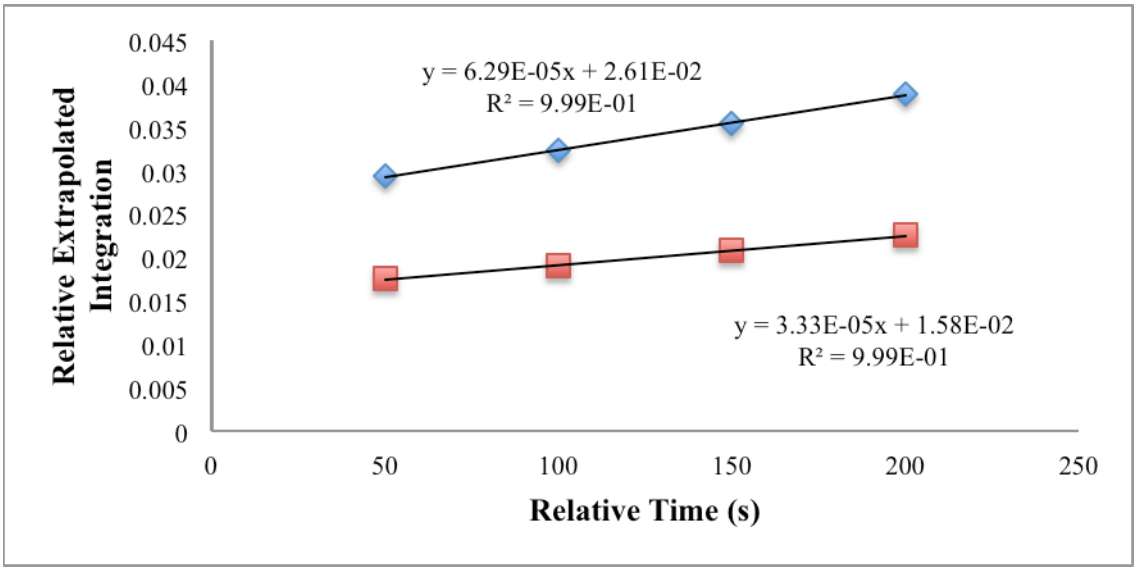


Representative plot for initial rate of formation of 3-fluoro-3-phenylpropyl acetate (*blue*) vs. 3-fluoro-3-phenylpropyl-3-*d* acetate (*red*) by ^{19}F NMR.

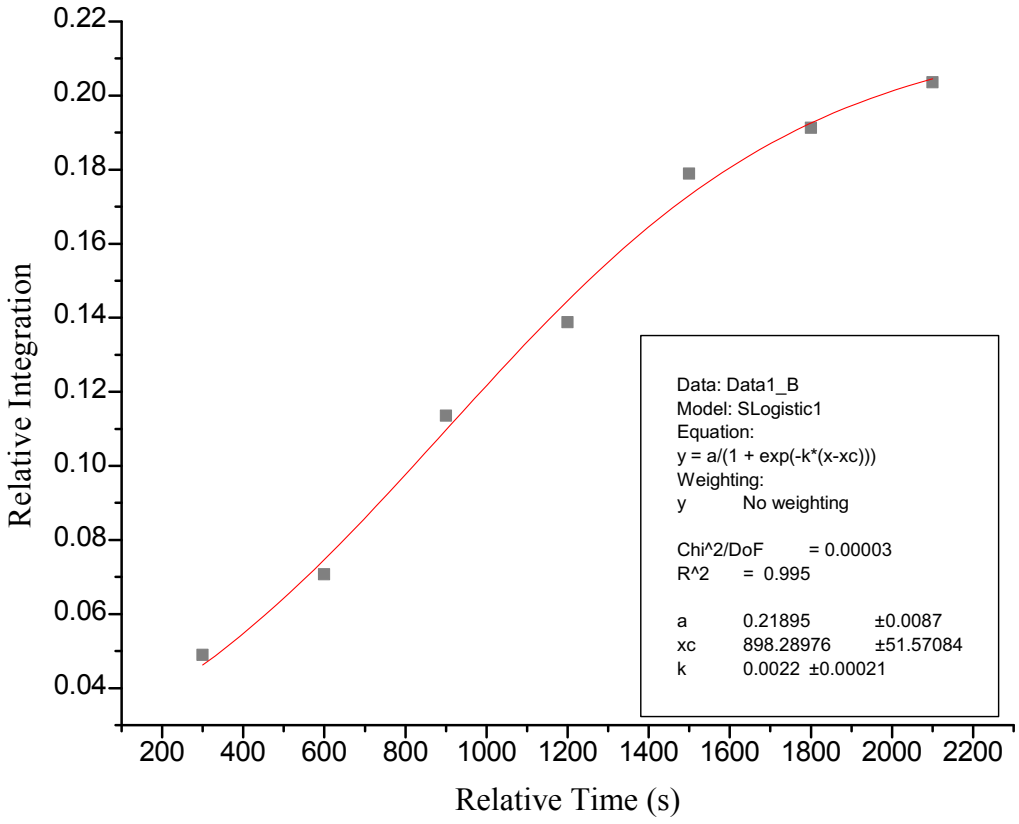
Competitive KIE: cyclohexane

Selectfluor (390 mg, 1.1 mmol), cuprous iodide (10 mg, 0.05 mmol), *N,N'*-bis(2,6-dichloro-benzylidene)ethane-1,2-diamine (19 mg, 0.05 mmol), and potassium carbonate (7 mg, 0.05 mmol) were added to a flame-dried 10 mL round bottom flask equipped with a stir bar under N_2. A degassed (with N_2) mixture of 4:1 CH_3CN:CD_3CN (6 mL) was added to the reaction flask, and the solution was immediately cooled to 0°C and stirred vigorously. After 10 minutes, 3-chlorobenzotrifluoride (0.02 mL, 0.15 mmol) was added via syringe. After 15 minutes, a 1:1 mixture of cyclohexane:cyclohexane-d_{12} (0.06 mL, 0.50 mmol) was added to the reaction flask. The reaction solution stirred for an additional 2

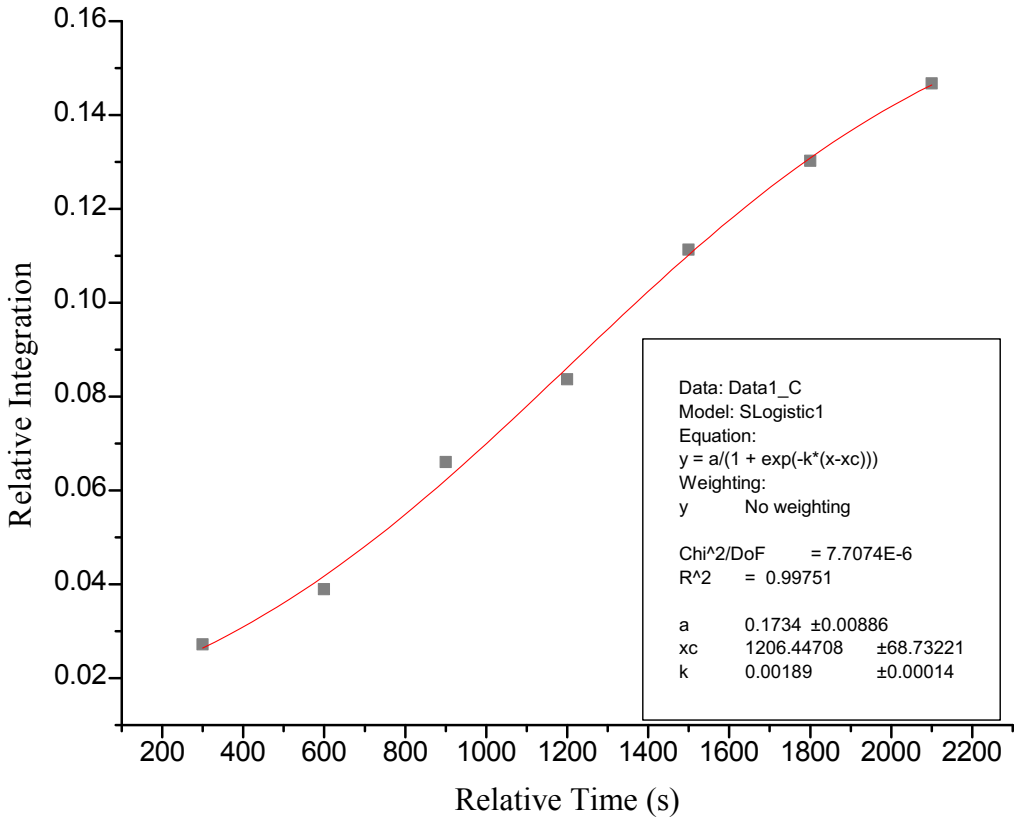
minutes, then 0.5 mL was transferred via syringe from the reaction flask to an NMR tube fit with a septum under N_2. A ^{19}F NMR spectrum of the same sample was collected every 300 seconds at 25°C. Product concentrations were determined using 3-chlorobenzotrifluoride as an internal standard. The data points were fitted to the equation of a sigmoidal curve (seen below) with high coefficients of determination, and this equation was used to extrapolate five points in the initial rate regime (within 600 s of first reported data point, as small peaks were observed 300 s and 600 s prior to the first reported data point, but could not be accurately integrated). All curves were fit/analyzed in the exact same manner. $k_H/k_D \approx 2.0$ (average of two runs: 1.9 + 2.1).



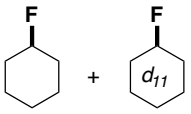
Representative plot for initial rate of formation of fluorocyclohexane (*blue*) vs. fluorocyclohexane-d_{11} (*red*) by ^{19}F NMR extrapolated from sigmoidal fit equations.

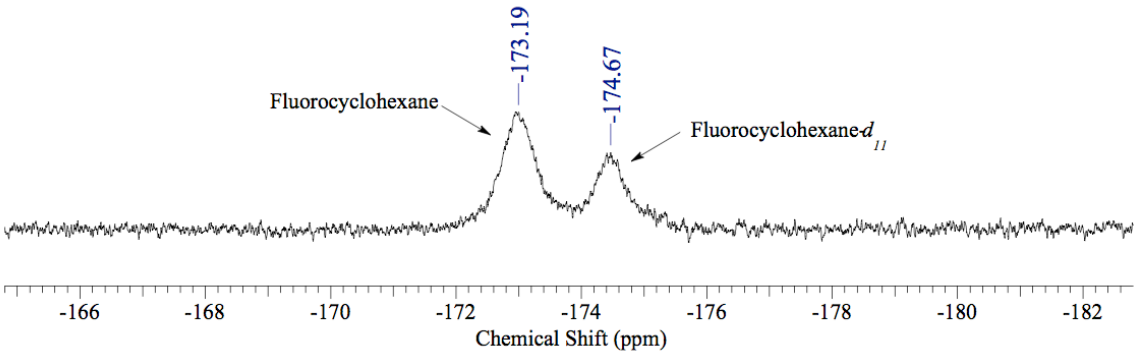


Sigmoidal fit for appearance of fluorocyclohexane by ^{19}F NMR.



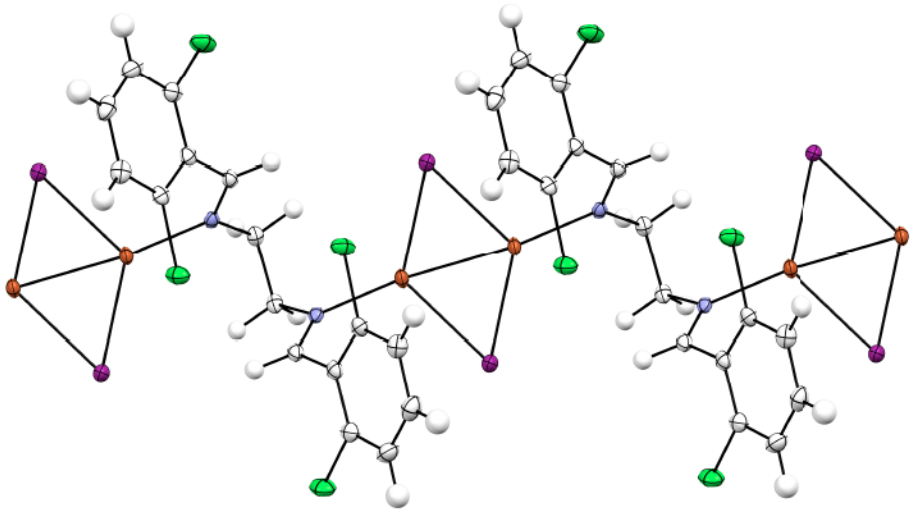
Sigmoidal fit for appearance of fluorocyclohexane-d_{11} by ^{19}F NMR.





Sample ^{19}F NMR of competitive KIE experiment following the rate of appearance of fluorocyclohexane vs. fluorocyclohexane-d_{11}.

Crystallographic Information



Displacement ellipsoid plot (50% probability level) of 2CuI□bis(imine) complex at 110(2) K.

An attempt was made to grow single crystals of the unoxidized copper-ligand complex. A yellow precipitate formed from a 1:1 mixture of cuprous iodide to ligand in MeCN after approximately 2 h of stirring. Upon filtration, dissolution, and solvent evaporation, single yellow crystals were obtained and suitable for X-ray structure determination. The crystal structure showed a polymeric complex exhibiting 2:1 cuprous iodide to ligand stoichiometry, copper atoms linked by bridging iodine atoms, and the nitrogen atoms on the ligand singly bound to two different copper atoms. The same compound was also isolated as more defined yellow microcrystals via the vapor diffusion technique with acetonitrile and diethyl ether.

Despite the tendency for these molecules to crystallize as a polymeric structure, we can quickly gather that this is unlikely playing any active role in solution during the reaction. In fact, the EPR signatures of the copper(II) species observed over the course of the reaction do not resemble those of dimeric or polymeric copper species.[291] This polymeric form is more likely just a thermodynamic sink for a copper-ligand interaction in its unoxidized form. Any attempt to grow crystals of the oxidized copper species (in the presence of Selectfluor) only afforded the ammonium salt - H-TEDA-BF_4 - previously reported by the Baran group.

All reflection intensities were measured at 110(2) K using a SuperNova diffractometer (equipped with Atlas detector) with Mo *K*α radiation (λ = 0.71073 Å) under the program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). The program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012) was used to refine the cell dimensions. Data reduction was done using the program CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). The structure was solved with the program SHELXS-2013 (Sheldrick, 2013) and was refined on F^2 with SHELXL-2013 (Sheldrick, 2013). Analytical numeric absorption corrections based on a multifaceted crystal model were applied using CrysAlisPro (Version 1.171.36.24 Agilent Technologies, 2012). The temperature of the data collection was controlled using the system Cryojet (manufactured by Oxford Instruments). The H atoms were placed at calculated positions using the

[291] For instance: Moncol, J.; Mudra, M.; Lönnecke, P.; Hewitt, M.; Valko, M.; Morris, H.; Svorec, J.; Melnik, M.; Mazur, M.; Koman, M. *Inorg. Chim. Acta.* **2007,** *360*, 3213-3225.

instructions AFIX 23 or AFIX 43 with isotropic displacement parameters having values 1.2 times *U*eq of the attached C atoms.

The structure is ordered.

Complex: Fw = 377.48, irregular yellow shaped crystals, 0.25 × 0.16 × 0.06 mm^3, monoclinic, *P*2/*c* (no. 13), *a* = 8.25345(18), *b* = 7.57776(17), *c* = 17.1862(3) Å, β = 94.4721(18)°, *V* = 1071.60(4) $Å^3$, *Z* = 4, D_x = 2.340 g cm^{-3}, μ = 5.368 mm^{-1}, abs. corr. range: 0.420–0.772. 9111 Reflections were measured up to a resolution of $(\sin \theta/\lambda)_{max}$ = 0.65 $Å^{-1}$. 2467 Reflections were unique (R_{int} = 0.0215), of which 2319 were observed [$I > 2\sigma(I)$]. 118 Parameters were refined. *R*1/*wR*2 [$I > 2\sigma(I)$]: 0.0167/0.0389. *R*1/*wR*2 [all refl.]: 0.0186/0.0398. S = 1.051. Residual electron density found between –0.40 and 0.46 e $Å^{-3}$.

Computational Methods

The Gaussian '09 package[292] and Spartan '06 were used for all calculations. All ^{19}F NMR calculated chemical shifts were fitted to the empirical equation (at B3LYP/6-311++G**) d_{calc} = -0.914d + 142.63. The isotropic values (d) employed were obtained from the CSGT calculation parameter found in the results menu. Geometry optimizations were determined at either B3LYP/6-311++G**, RI-MP2/6-311++G**, B3PW91/6-311++G**, or DGDZVP/6-311++G** (employed for Cu and I) using the default acetonitrile solvent continuum. Transition states

[292] Huczynski, A.; Rutkowski, J.; Brzezinski, B. *Struct. Chem.* **2011,** *22*, 627-634.

were determined at the B3LYP/6-311++G** level of theory using the default acetonitrile s

12.7) EXPERIMENTAL DETAILS FOR CHAPTER 8

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and compounds were dried and/or distilled by standard methods. ^{1}H spectra were acquired on a 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ -64.2 ppm relative to $CFCl_3$). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]). High resolution mass spectra (HRMS) were recorded using ESI-TOF (electrospray ionization-time of flight) mass spectrometry. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 3-fluorocyclohex-1- ene **(85)**,[293] 3-fluorocyclooct-1-ene **(87)**,[294] 3-fluorocyclododec-1-ene **(84)**,[295] 3-fluorohexa-1,5-diene and 6-fluorohexa-1,4-diene **(88)**, [296 ,298] 3-fluoro-2,3-dimethylbut-1-ene **(89)**, [297] 7- fluorotetradecene **(90)**,[295] 1-fluoro-1H-indene **(92)**, [298] and (1-

[293] Lee, E.; Yandulov, D. V. *J. Fluorine Chem*. **2009,** *130*, 474-483.
[294] Haufe, G.; Alvernhe, G.; Anker, D.; Laurent, A.; Saluzzo, C. *J. Org. Chem*. **1992,** *57*, 714-719.
[295] Barney, C. L.; Matthews, D. P.; McCarthy, J. R. *Tetrahedron Lett*. **1990,** *31*, 973-976.
[296] Dolbier, W. R.; Medinger, K. S.; Greenberg, A.; Liebman, J. F. *Tetrahedron* **1982,** *38*, 2415-2420.
[297] DesMarteau, D. D.; Xu, Z.-Q.; Witz, M. *J. Org. Chem*. **1992,** *57*, 629-635.
[298] Barnette, W. E. *J. Am. Chem. Soc.* **1984,** *106*, 452-454.

fluoroallyl)benzene **(94)** [298,299] were consistent with the literature precedents. Spectral data was processed with ACD/NMR Processor Academic Edition.[267] Compounds were purified by column chromatography on neutral alumina, eluting with pentane, and evaporating the solvent under reduced pressure at 0°C. Characterization data for these compounds are reported in residual pentane due to product volatility.

General Procedure for the allylic fluorination of alkenes:

An oven-dried, 10 ml round bottom flask equipped with a stir bar was placed under an atmosphere of N_2. PhSeCl (58.0 mg, 0.30 mmol, 1.20 equiv), AgF (95.0 mg, 0.75 mmol, 3.0 equiv), and *N*-fluoropyridinium tetrafluoroborate (102 mg, 0.55 mmol, 2.2 equiv) were added followed by CH_2Cl_2 (3.0 ml). 3-fluorocyclododec-1-ene was then added and the mixture allowed to stir overnight. The resulting suspension was filtered through celite and the organics washed with 1M HCl, saturated $NaHCO_3$ (aq), cold 30% H_2O_2 (aq) and saturated $Na_2S_2O_8$ (aq). The organics were further dried with $MgSO_4$ and filtered through celite. The solvent was removed by rotary evaporation and the crude residue columned on neutral alumina using hexanes as eluent.

Preparation of *d_2*-cyclooctene:

Synthesis of Cyclooctyne:

[299] Doyle, A. G.; Katcher, M. H.; Sha, A. *J. Am. Chem. Soc.* **2011,** *133*, 15902-15905.

Cyclooctyne was prepared according to Brandsma et al.[300] Bromine (7.0 mL, 21.7 g, 0.272 mol) was added drop-wise to a solution of cyclooctene (17.7 mL, 15.0 g, 0.136 mol) in 50 mL of CH_2Cl_2 cooled to -40°C, until no further color change was evident. The reaction mixture was then washed with 10% $Na_2S_2O_4$ (2 x 100 mL) and CH_2Cl_2. The combined organic extracts were washed with H_2O (50 mL), brine (50 mL), and dried with MgSO4. Vacuum filtration through celite followed by rotary evaporation yielded the vicinal dibromide as a yellow oil. This oil was immediately dissolved in 60 mL of diethyl ether and chilled to 0°C. Sodium tert-butoxide (19.6 g, 0.204 mol) dissolved in 30 mL of THF was then added using a drop funnel. An immediate color change was observed, and the solution was left to stir overnight. The reaction mixture was poured into a separatory funnel along with 100 mL of ice water. The phases were separated, and the aqueous phase washed with ether (2 x 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. Subsequent filtration, rotary evaporation, and distillation under vacuum yielded the vinyl bromide as a clear liquid (11.7 g, 0.0619 mol).

A solution of lithium diisopropylamide was prepared through dropwise addition of n-butyllithium (1.6M in hexanes, 19.4 mL, 0.031 mol), to a solution of diisopropylamine (4.51 mL, 3.24 g, 0.033 mol) in 13 mL of THF at -25°C. The solution was allowed to stir for an hour at -25°C before returning to room temperature. Once at room temperature the reaction mixture was cooled again to -25°C and 1-bromocyclooctene added drop-wise. The resulting solution was

[300] Brandsma, L.; Verkruusse, H.D. *Synthesis Comm.* **1977,** 290-293.

allowed to stir overnight and slowly warm to room temperature. The reaction mixture was neutralized with 15 mL 3M HCl, followed by extraction with pentane (5 x 20 mL). The combined organic extracts were washed with H_2O, brine, and dried with $MgSO_4$. Vacuum filtration followed by rotary evaporation at 0°C provided a yellow oil, cyclooctyne, which was further purified by distillation under reduced pressure.

Synthesis of 1,2-dideuterocyclooctene:

1,2-dideuterocyclooctene was prepared by reduction of cyclooctyne with $LiAlD_4$ following the procedure reported by Coseri et al.[301] Cyclooctyne (1.6 mL, 1.4 g, 0.013 mol) was added dropwise at 0°C to a 1M solution of lithium aluminum deuteride in THF (1M, 14mL, 0.014 mol). The mixture was brought to reflux and allowed to reflux overnight. Once cooled, the reaction mixture was quenched with D_2O (5 mL), and DCl (20% in D_2O, 20 mL). The organic layer was washed with H_2O (5 x 5 mL), and dried with $MgSO_4$. Vacuum filtration followed by removal of the solvent at 0°C afforded a crude oil which was distilled under vacuum to afford the dideuteratoalkene as a clear colorless liquid.

Characterization:

3-fluorocyclohept-1-ene (86). ^{1}H NMR ($CDCl_3$): δ 5.98-5.76 (dm, 2H), 5.30-5.04 (dm, 1H), 2.42-1.20 (m, 8H); ^{19}F NMR (CDCl3): δ -167.0 (br d, *J* = 49 Hz, 1F); HRMS-(ESI$^+$) calcd for $C_7H_{11}FNa^+$: 137.0232, found 137.0247.

[301] Coseri, S.; Mendenhall, G.D.; Ingold, K.U. *J. Org. Chem.* **2005,** *70*, 4629-4636.

3-fluorocyclododec-1-ene (84). ^{1}H NMR ($CDCl_3$): δ 5.82-5.43 (dm, 2H), 5.02-4.75 (dm, 1H), 2.36-1.83 (m, 4H), 1.34-1.24 (m, 14H); ^{19}F NMR ($CDCl_3$): δ168.0 (br d, *J* = 49 Hz, 1F).

7-fluorotetradecene (90). ^{1}H NMR ($CDCl_3$): δ 5.86-5.45 (dm, 2H), 4.96-4.67 (dm, 1H), 2.17-2.01 (m, 4H), 1.49-1.22 (m, 12H), 0.99-0.82 (m, 8H); ^{19}F NMR ($CDCl_3$): δ -171.0 (m, 1F).

N-(4-fluoro-4-methylpent-2-enyl) phthalimide (91). ^{1}H NMR ($CDCl_3$): δ 7.76 (m, 2H), 7.65 (m, 2H), 5.80-5.62 (m, 2H), 4.22-4.15 (m, 2H), 1.32 (d, *J* = 20 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 167.8, 135.5, 133.8, 132.2, 123.2 (d, *J* = 18 Hz), 114.3, 95.9 (d, *J* = 180 Hz), 39.3, 18.2; ^{19}F NMR ($CDCl_3$): δ -135.3 (sp x 2, *J* = 22, 12 Hz, 1F); HRMS-(ESI^{+}) calcd for $C_{14}H_{14}FNO_2Na^{+}$: 270.1275, found 270.1263.

1-fluoro-1H-indene (92). ^{1}H NMR ($CDCl_3$): δ 7.48-7.13 (m, 4H), 6.89-6.73 (m, 2H), 5.95 (dd, *J* = 53, 3 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ -201.0 (br d, *J* = 50 Hz, 1F).

(R)-7-fluoro-3-methyl-5-octenyl benzoate (93). ^{1}H NMR ($CDCl_3$): δ 7.54-7.26 (m, 4H), 7.19-7.11 (m, 1H), 5.61-5.47 (m, 2H), 4.34-4.13 (m, 2H), 2.17-1.03 (m, 8H), 1.31 (d, *J* = 21 Hz, 6H); ^{13}C NMR ($CDCl_3$): 165.6, 134.7 (d, *J* = 22 Hz), 132.0, 130.6, 128.6, 127.5, 126.5 (d, *J* = 11 Hz), 92.9 (d, *J* = 162.0 Hz), 62.5, 38.6, 34.2, 29.3, 26.4 (d, *J* = 25 Hz), 18.4; ^{19}F NMR ($CDCl_3$): δ -132.4 (sp x 2, *J* =

21, 12 Hz, 1F). HRMS-(ESI$^+$) calcd for $C_{17}H_{23}FO_2Na^+$: 301.2243, found 301.2251.

12.8) EXPERIMENTAL DETAILS FOR CHAPTER 9

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and compounds were dried and/or distilled by standard methods. ^{1}H spectra were acquired on a 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ -64.2 ppm relative to $CFCl_3$). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]). IR data were obtained using an FT-IR and standard NaCl cell. High resolution mass spectra (HRMS) were recorded using ESI- TOF (electrospray ionization-time of flight) mass spectrometry. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 1-fluoroadamantane (**32**),[302] 1-fluorocyclododecane (**35**),[303] fluorobicyclo[2.2.1]heptane (**98**),[304] 1-fluorocycloheptane (**36**),[303],[305] 1-

[302] Aoyama, M.; Fukuhara, T.; Hara, S. *J. Org. Chem*. **2008,** *73*, 4186-4189.
[303] (a) Amaoka, Y.; Nagatomo, M. Inoue, M. *Org. Lett*. **2013,** 15, 2160-2163. (c) Olah, G. A.; Li, X.-Y.; Wang, Q.; Surya Prakash, G. K. *Synthesis* **1993**, *7*, 693-699. (d) Schneider, H.-J.; Gschwendtner, W.; Heiske, D.; Hoppen, V.; Thomas, F. *Tetrahedron* **1977,** *33*, 1769-1773.
[304] (a) Namavari, M.; Satyamurthy, N.; Barrio, J. R. *J. Fluorine Chem*. **1995,** *72*, 89-93. (b) Adcock, W.; Abeywickrema, A. N.; Kok, G. B. *J. Org. Chem.* **1984,** *49*, 1387-1397. (c) Bradshaw, T. K.; Hine, P. T.; Della, E. W. *Org. Mag. Res*. **1981,** *16*, 26-27. (d) Shackelford, S. A. *J. Org. Chem*. **1979**, *44*, 3485-3491. (e) Roberts, J. D.; Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A. *J. Am. Chem. Soc*. **1970,** *92*, 7107-7110.
[305] Bucsi, I.; Török, B.; Marco, A. I.; Rasul, G.; Surya Prakash, G. K.; Olah, G. A. *J. Am. Chem. Soc.* **2002,** *124*, 7728-7736.

fluorocyclooctane (**37**),[306] 1-fluorocyclohexane (**99**),[307] fluorododecane (**41**),[308] 1-fluoroundecanoic δ-lactone (**47**),[103] and fluorosclareolide (**100**)[104] were consistent with the literature precedents. Spectral data was processed with ACD/NMR Processor Academic Edition.[267]

Experimental Setup:

Starting materials and acetonitrile were placed in a *Fisherbrand* 13 x 100 mm culture tube, sealed with a septum/copper wire, and placed under an atmosphere of N_2. The culture tubes were then arranged in a beaker making sure to fill empty spaces with additional culture tubes. Once arranged, a UV Pen lamp (302 nm) was placed in a separate culture tube and the beaker filled halfway with water. At this point, the setup was covered by aluminum foil and the samples irradiated for 16 h.

Fluorination of α-santonin:

To an 13 x 100 mm glass culture tube equipped with a stir bar and septum was placed α- santonin (61.6 mg, 0.25 mmol, 1.0 equiv) under an atmosphere of N_2 followed by MeCN (3.0 ml). Control experiments were performed in the presence and in the absence of the following: Selectfluor (195 mg, 0.55 mmol,

[306] (a) Srivastava, V. P.; Yadav, A. K.; Yadav, L.; Dhar, S. *Chem. Commun.* **2013,** *49*, 2154-2156. (b) Lheureux, A.; Bequlieu, F.; Laflamme, F.; Couturier, M.; Bennett, C.; Clayton, S.; Tovell, D.; Bill, D. R.; Mirmehrabi, M.; Tadayon, S. *J. Org. Chem.* **2010,** *75*, 3401-3411.
[307] Chambers, R. D.; Kenwright, A. M.; Parsons, M.; Sandford, G.; Moilliet, J. S. *J. Chem. Soc., Perkin Trans. 1* **2002,** *19*, 2190-2197.
[308] Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S. *Tetrahedron* **2004,** *60*, 6923-6930.

2.2 equiv), 1,2,4,5-tetracyanobenzene (4.45 mg, 0.025 mmol, 0.1 equiv), UV irradiation (302 nm) and previously isolated fluorosantonin (**101**). Products were determined either by NMR spectroscopy or column chromatography on silica.

Fluorination of α, β-unsaturated aryl ester:

To an 13 x 100 mm glass culture tube equipped with a stir bar and septum was placed α,β-unsaturated aryl ester (58.1 mg, 0.25 mmol, 1.0 equiv) under an atmosphere of N_2, Selectfluor (195 mg, 0.55 mmol, 2.2 equiv) and 1,2,4,5-tetracyanobenzene (4.45 mg, 0.025 mmol, 0.1 equiv), were then added, followed by MeCN (3.0 mL). The reaction mixture was then placed in a water bath and irradiated using a UV Pen Lamp at 302 nm for 16 h. Product identity and yields were determined by ^{19}F NMR spectroscopy in comparison to known literature values and 3-chlorobenzotrifluoride as an internal standard.

Characterization:

1-fluorocyclodecane (38). Clear oil. ^1H NMR ($CDCl_3$): δ 4.81 (brd, *J* = 46 Hz, 1H), 2.15- 1.42 (m, 6H), 1.39-1.19 (m, 2H), 1.02-0.79 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 93.2 (d, *J* = 155 Hz), 31.1, 30.9, 30.7, 29.7, 29.4, 24.1, 23.7, 21.0, 20.9; ^{19}F NMR ($CDCl_3$): δ – 166.4 (m, 1F). Isolation and subsequent characterization of **6** proved difficult due to product volatility. For additional characterization data see: Matsui, T.; Deguchi, M.; Yoshizawa, H. *U.S. Pat. Appl. Publ.* **2005,** US 20050158623 A1 20050721.

1-fluorocycloundecane (40). Clear oil. ^{1}H NMR ($CDCl_3$): δ 4.72 (brd, *J* = 47 Hz, 1H), 2.13-1.19 (m, 1H), 1.87-1.70 (m, 2H), 1.64-1.16 (m, 6H), 0.95-0.78 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 94.7 (d, *J* = 165 Hz), 32.8, 32.7, 29.7, 26.5, 26.2, 26.0, 25.7, 25.3, 22.4, 22.3; ^{19}F NMR ($CDCl_3$): δ – 166.4 (m, 1F); HRMS-(ESI^+) calcd for $C_{11}H_{21}FNa^+$: 195.1454, found 195.1463.

Fluorosantonin (101). Amorphous solid. ^{1}H NMR ($CDCl_3$): δ 6.74 (d, *J* = 10 Hz, 1H), 6.33 (d, *J* = 10 Hz, 1H), 5.58 (dd, 48, 16 Hz, 1H), 5.56 (dd, 48, 16 Hz, 1H), 4.86 (dd, *J* = 11.3, 6.7 Hz, 1H), 2.46 (dq, *J* = 12.2, 6.9 Hz, 1H), 2.13-1.55 (m, 5H), 1.42 (s, 3H), 1.3 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 184.2, 176.7, 158.6, 154.8, 127.3 (d, *J* = 14.6 Hz), 126.2, 80.8, 74.5, 72.9, 53.8 (d, *J* = 2.2 Hz), 40.9, 38.2, 36.6, 25.3 (d, *J* = 1.5 Hz), 24.7, 23.1, 12.5; ^{19}F NMR ($CDCl_3$): δ – 207.5 (dt, *J* = 93.3, 47.4 Hz, 1F); IR (CH_2Cl_2): 1782, 1661, 1627, 1618 cm^{-1}; HRMS-(ESI^+) calcd for $C_{15}H_{17}FO_3Na^+$: 287.1054, found 287.1095.

3-fluoroadamantan-1-ylisoindoline-1,3-dione (102). Amorphous solid. ^{1}H NMR ($CDCl_3$): δ 7.85-7.69 (dm, 4H), 2.69 (m, 4H), 2.60-2.53 (m, 1H), 2.35 (s, 2H), 2.30-2.08 (m, 2H), 2.0-1.84 (m, 4H), 1.3 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 169.1, 134.1, 131.5, 123.0, 93.2 (d, *J* = 14.6 Hz), 91.3 (d, *J* = 14.6 Hz), 61.2, 47.2 (t, *J* = 19.2 Hz), 44.2 (dt, *J* = 19.4, 5.5 Hz), 40.1, 37.5, 29.2 (t, *J* = 11.2 Hz); ^{19}F NMR ($CDCl_3$): δ – 136.5 (s, 1F); IR (CH_2Cl_2): 1640 cm^{-1}; HRMS-(ESI^+) calcd for $C_{18}H_{18}FNO_2Na^+$: 322.1154 , found 322.1151.

2,2,2-trifluoro-*N*-(fluorocyclohexyl)-*N*-isopropylacetamide (103). Clear oil. ^{1}H NMR ($CDCl_3$): δ 5.02 (bd, *J* = 48 Hz, 2H), 4.87 (bd, *J* = 48 Hz, 1H), 4.56 (dm, *J* = 49 Hz, 1H), 4.27-3.96 (m, 2H), 3.80-3.47 (m, 2H), 3.31-3.13 (m, 1H), 2.78-2.18 (m, 3H), 2.06-1.46 (m, 18H), 1.42-1.30 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 96.8, 96.6, 95.8, 94.9, 94.2, 93.1, 91.8, 91.4, 61.6, 59.4, 57.8, 55.3, 55.0, 54.9, 54.8, 53.6, 53.4, 40.4, 40.1, 39.9, 36.8, 35.3, 35.1, 34.8, 34.7, 34.6, 34.5, 34.3, 34.1, 33.1, 32.4, 29.6, 28.0, 25.0, 24.9, 24.8, 24.6, 24.2, 24.1; ^{19}F NMR ($CDCl_3$): δ -64.0 (s, 3F), -64.1 (s, 3F), -64.2 (s, 3F), -64.3 (s, 3F), 64.4 (s, 3F), -163.3 (bd, *J* = 50 Hz, 0.5H), -163.6 (bd, *J* = 50 Hz, 0.5H), -179.0 to -180 (m, 3H), - 181.3 (m, 1H); IR (CH_2Cl_2): 1685 cm^{-1}; HRMS-(ESI$^+$) calcd for $C_{11}H_{17}F_4NONa^+$: 278.1092, found 278.1088.

12.9) EXPERIMENTAL DETAILS FOR CHAPTER 10

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and compounds were dried and/or distilled by standard methods. ^{1}H spectra were acquired on a 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ -64.2 ppm relative to $CFCl_3$). NMR data are reported in the following format: chemical shift (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), integration, coupling constants [Hz]). Spectral data was processed with ACD/NMR Processor Academic Edition.[267] Compounds **44,**[309] **104,**[309] **105,**[310] **107,**[311] **109,**[312] **51,**[313] **59,**[309] **110,**[314] **63,**[315] **111,**[316,317,318] and **112**[319,320] are in agreement with previously reported spectral data.

Experimental Setup:

Benzylic substrate (0.25 mmol), Selectfluor (0.55 mmol, 195.0 mg, 2.2 equiv), 1,2,4,5-tetracyanobenzene (0.025 mmol, 4.5 mg, 0.1 equiv) and acetonitrile (3 ml) were placed in a Biotage 5 mL microwave reaction vial, sealed with a septum cap, and placed under an atmosphere of N_2. Samples were placed in a beaker, covered in aluminum foil, and irradiated with a UV pen lamp (302 nm) for 16

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[312] Kobayashi, S.; et. al., *Tetrahedron*, 2004, **60**, 6923-6930.
[313] Ramsden, C. A.; Shaw, M. M., *Tetrahedron Lett*., 2009, **50**, 3321-3324.
[314] Oldendorf, J.; Haufe, G.; *Adv. Synth. Catal*., 2000, **342**, 52-57.
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[316] Butt, G.; et. al., *Spectrochim. Acta Mol. Biomol. Spectros*., 1980, **36**, 521-524.
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[318] Brownlee, R.; Craik, D., *Tetrahedron Lett*., 1980, **21**, 1681-1684.
[319] Busci, I.; et. al., *J. Am. Chem. Soc*., 2002, **124**, 7728-7736.
[320] Johnson, A., *J. Org. Chem*., 1982, **47**, 5220-5222.

hours. Products were extracted in dichloromethane and washed with water. The organics were dried with $MgSO_4$ and filtered through celite. The solvents were removed by rotary evaporation and the residue subjected to column chromatography on florisil with a mixture of ethyl acetate/hexanes as eluent.

Volatile Substrates:

Substrates **44**, **104**, **105**, and **51** were extracted into diethyl ether and washed with water. The organics were dried with $MgSO_4$ and filtered through celite. Rotary evaporation at 0^oC was used to remove solvent. No further purification was used to remove excess starting material. Crude NMR spectra were collected with a 1s presaturation pulse on the residual acetonitrile solvent.

Characterization:

(1-fluoroethyl)benzene (44). ^1H NMR ($CDCl_3$): δ 7.46-7.11 (m, 5H), 5.6 (dq, 1H, J = 47.7, 6.4 Hz), 1.35 (dd, 3H, J = 23.7, 6.0); ^{19}F NMR ($CDCl_3$): δ -166.3 (dq, 1F, J = 47.4, 23.7 Hz). (65% yield).

(2-fluoropropan-2-yl)benzene (104). Spectral and analytical data were in agreement with previous reports.[309,320] (37% yield).

(fluoromethyl)benzene (105). ^1H NMR ($CDCl_3$): δ 7.42-7.33 (m, 5H), 5.38 (d, 2H, J = 47.9 Hz); ^{19}F NMR ($CDCl_3$): δ -206.1 (t, 1F, J = 47.0 Hz). (46% yield).

3-fluoro-3-phenylpropanal (106). ^1H NMR ($CDCl_3$): δ 9.87 (m, 1H), 7.48-7.35 (m, 5H), 6.12-6.04 (ddd, 1H, J = 47.1, 8.6, 3.9 Hz), 3.27-2.84 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 198.5 (s), 138.6 (s), 128.93 (s), 128.9 (s), 128.8 (s), 125.5 (s), 125.4 (s), 89.1 (d, J = 171.8 Hz) 50.7 (s), 50.4 (s). ^{19}F NMR ($CDCl_3$): δ -173.8 (ddd, 1F, J = 47.0, 31.0, 17.2 Hz). (59% yield).

methyl 2-(1,3-dioxoisoindolin-2-yl)-3-fluoro-3-phenylpropanoate (107). ^1H

NMR ($CDCl_3$): δ 8.17- 7.07 (m, 18H), 6.39 (dd, 1H, *J* = 46.9, 7.2 Hz), 6.25 (dd, 1H, *J* = 46.95, 8.0 Hz), 5.38-5.14 (m, 2H), 3.85 (s, 3H), 3.71 (s, 3H). ^{19}F NMR ($CDCl_3$): δ -177.3 (dd, 1F, *J* = 47.4, 13.4 Hz), -169.5 (dd, 1F, *J* = 47.5, 15.5 Hz). (62% yield).

(*E*)-5-fluoro-5-phenylpent-2-enoic acid (108). ^{1}H NMR ($CDCl_3$): δ 7.39-6.92 (m, 6H), 5.78 (d m, 1H), 5.51 (ddd, 1H, *J* = 47.9, 8.1, 4.7 Hz), 2.79-2.68 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 170.83 (s), 150.70 (s), 128.74 (s), 128.67 (s), 128.53 (s), 128.34 (s), 121.21 (s), 93.28 (d, *J* = 174.9 Hz), 40.63 (s). ^{19}F NMR ($CDCl_3$): δ -174.7 (ddd, 1F, *J* = 46.4 Hz). (53% yield).

Methyl 2-(4-(1-fluoro-2-methylpropyl)phenyl)propanoate (53). ^{1}H NMR ($CDCl_3$): δ 7.35-7.21 (m, 5H), 5.10 (dd, 1H, *J* = 47.1, 6.8 Hz), 3.82-3.70 (m, 1H), 3.66 (s, 3H), 2.18-1.99 (m, 1H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.02 (dd, 3H, *J* = 6.6, 0.9 Hz), 0.87 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 175.0 (s), 174.9 (s) 140.4 (s), 138.4 (s), 138.2 (s), 130.6 (s), 127.3 (s), 126.5 (s), 99.0 (d, *J* = 175 Hz), 96.3 (s), 52.0 (s), 47.3 (s), 45.2 (s), 45.1 (s), 34.4 (s), 34.1 (s), 26.8 (s), 26.5 (s), 18.6 (s), 18.4 (s), 18.3 (s) 17.6 (s), 17.5 (s); ^{19}F NMR ($CDCl_3$): δ -179.8 (ddd, 1F, *J* = 47.4, 16.5, 6.2 Hz). (64% yield).

1-bromo-4-(fluoromethyl)benzene (109). ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H, *J* = 8.3 Hz), δ 7.26 (dd, 2H, *J* = 8.1, 1.5 Hz), 5.36-5.20 (d, 2H, *J* = 47.3 Hz). ^{19}F NMR ($CDCl_3$): δ -207.6 (t, 1F, *J* = 47.4 Hz). (36% yield).

1-(fluoromethyl)-4-isopropylbenzene (51). ^{19}F NMR ($CDCl_3$): δ -203.1 (t, 1F, *J* = 48.5 Hz). (41% yield).

4-(fluoromethyl)-1,1'-biphenyl (59). ^{1}H NMR ($CDCl_3$): δ 7.69-7.59 (m, 4H), 7.52-7.44 (m, 4H), 7.42-7.36 (m, 1H), 5.46 (d, 2H, *J* = 47.9 Hz); ^{19}F NMR ($CDCl_3$): δ -205.2 (t, 1F, *J* = 47.4 Hz). (52% yield).

(1-fluoro-2-(phenylsulfonyl)ethyl)benzene (66). ^{1}H NMR ($CDCl_3$) δ 8.0–7.63 (m, 10H), 6.04 (ddd, 1H, *J* = 47.5, 9.4, 2.5 Hz), 3.83 (ddd, 1H, *J* = 22.8, 13.4, 1.7 Hz), 3.49 (ddd, 1H, *J* = 31.7, 15.3, 2.5 Hz); ^{13}C NMR (CDCl3) δ 139.1 (s), 137.5 (s), 133.9 (s), 133.8 (s), 129.4 (s), 129.3 (s), 128.9 (s), 128.8 (s), 128.3 (s), 128.1 (s), 126.9 (s), 125.5 (d, *J* = 6.6 Hz), 88.5 (d, *J* = 177.1 Hz), 62.7 (d, *J* = 26.4 Hz); ^{19}F NMR ($CDCl_3$) δ –172.1 (ddd, 1F, *J* = 47.4, 32.0, 13.4 Hz). (43% yield).

1-fluoro-1,5-diphenylpentan-3-one (67). ^{1}H NMR ($CDCl_3$) δ 7.50–7.12 (m, 10H), 6.01 (ddd, 1H, *J* = 47.5, 8.3, 4.0 Hz), 3.2 (ddd, 1H, *J* = 23.4, 14.3, 2.5 Hz), 3.0–2.7 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 205.8 (s), 142.6 (s), 140.7 (s), 139.2 (s), 139.0 (s), 128.9 (s), 128.7 (s), 128.6 (s), 128.5 (s), 128.3 (s), 125.8 (d, *J* = 5.9 Hz), 125.4 (s), 90.1 (d, *J* = 171 Hz), 50.1 (d, *J* = 25.6 Hz), 42.2 (s), 29.4 (s); ^{19}F NMR ($CDCl_3$) δ –173.4 (ddd, 1F, *J* = 46.4, 32.0, 14.4 Hz). (61% yield).

3-fluoro-1,3-diphenylpropan-1-one (55). ^{1}H NMR ($CDCl_3$): δ 8.10-7.30 (m, 10H), 6.21 (ddd, 1H, *J* = 46.5, 8.1, 4.1 Hz), 3.83 (ddd, 1H, *J* = 17.0, 14.9, 8.3), 3.35 (ddd, 1H, *J* = 29.6, 17.0, 4.1); ^{13}C NMR ($CDCl_3$): δ 190.6 (s), 144.8 (s), 139.7 (s), 139.4 (s), 136.7 (s), 133.5 (s), 132.8 (s), 130.5 (s), 129.0 (s), 128.7 (s), 128.2 (s), 125.7 (s), 125.6 (s), 122.2 (s), 90.3 (d, *J* = 170 Hz), 46.2 (s), 45.8 (s); ^{19}F NMR ($CDCl_3$): δ -173.0 (ddd, 1F, *J* = 46.4, 29.9, 15.5 Hz). (58% yield).

2-fluoro-2-phenylethyl acetate (110). ^{1}H NMR ($CDCl_3$): δ 7.46-7.37 (m, 5H), 5.76-5.58 (ddd, 1H, *J* = 48.9, 6.5, 4.7 Hz), 4.43-4.33 (m, 2H), 2.14 (s, 3H). ^{19}F NMR ($CDCl_3$): δ -183.8 (ddd, 1F, *J* = 49.3, 26.4, 23.0 Hz). (55% yield).

3-fluoro-3-phenylpropanoic acid (64). ^{1}H NMR ($CDCl_3$) δ 11.9 (br s, 1H), 7.51–7.37 (m, 5H), 6.06-5.87 (ddd, 1H, *J* = 46.8, 9.2, 3.9 Hz), 3.19-3.07 (ddd, 1H, *J* = 16.4, 13.5, 9.3 Hz), 2.98-2.82 (ddd, 1H, *J* = 32.5, 16.2, 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2 (s), 138.4 (s), 138.2 (s), 129.0 (s), 128.8 (s), 128.6 (s), 128.3 (s),

125.7 (s), 90.4 (d, J = 172.5 Hz), 42.3 (s), 42.1 (s); ^{19}F NMR ($CDCl_3$) δ –172.4 (ddd, 1F, J = 46.4, 33.0, 13.4 Hz). (52% yield).

3-fluoro-3-phenylpropanenitrile (63). Spectral and analytical data were in agreement with previous reports.[312] (47% yield).

4-(fluoromethyl)benzonitrile (111). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H, J = 8 Hz), 7.49 (d, 2H, J = 8 Hz), 5.48 (d, 2H, J = 47.2 Hz). ^{19}F NMR (CDCl3): δ -214.6 (t, 1F, J = 47.0 Hz). (28% yield).

(fluoromethanetriyl)tribenzene (112). ^{1}H NMR ($CDCl_3$): δ 7.41-7.32 (m, 9H), 7.30-7.22 (m, 6H); ^{19}F NMR (CDCl3): δ -125.4 (s, 1F). (34% yield).

%chk=2-phenylethyl acetaterasdcat6a.chk

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opt pbepbe/cc-pvtz scrf=(solvent=acetonitrile) maxdisk=29GB geom=con
nectivity

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-1.626274	-2.295252	-0.352197
2	6	0	-1.942053	-1.265977	-0.177161
3	6	0	-2.719828	1.393850	0.294549
4	6	0	-1.031930	-0.353025	0.418706
5	6	0	-3.223129	-0.860670	-0.507668
6	6	0	-3.616401	0.470838	-0.275059
7	6	0	-1.436906	0.993059	0.623247
8	1	0	-3.927364	-1.566384	-0.946616
9	1	0	-4.621101	0.792747	-0.549645
10	1	0	-0.730456	1.702264	1.055160
11	1	0	-3.036657	2.421353	0.469428
12	6	0	0.302095	-0.799233	0.827210
13	1	0	0.353642	-1.874721	1.028553
14	1	0	0.717095	-0.215865	1.657244
15	6	0	1.424640	-0.601401	-0.380456

16	1	0	1.059059	-1.225855	-1.212666
17	8	0	2.642736	-1.066083	0.064093
18	6	0	3.446609	0.100508	0.397987
19	1	0	4.494003	-0.157781	0.215398
20	1	0	3.300040	0.339516	1.462022
21	8	0	1.506986	0.734381	-0.719925
22	6	0	2.890360	1.157263	-0.542058
23	1	0	2.885048	2.169626	-0.126639
24	1	0	3.374452	1.152699	-1.529165

Rotational constants (GHZ): 2.5346093 0.4952606 0.4500061

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%chk=2-phenylethyl acetaterasdcat.chk

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opt upbepbe/cc-pvtz scrf=(solvent=acetonitrile) maxdisk=29GB geom=co
nnectivity

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-1.120659	-1.960237	0.275475
2	6	0	-1.777901	-1.097998	0.174955
3	6	0	-3.476323	1.145754	-0.052703
4	6	0	-1.231859	0.186544	-0.114773
5	6	0	-3.139969	-1.254682	0.324264
6	6	0	-3.998164	-0.136056	0.213761
7	6	0	-2.115114	1.308269	-0.204112
8	1	0	-3.560387	-2.237281	0.533769
9	1	0	-5.072037	-0.266517	0.346604
10	1	0	-1.693213	2.292358	-0.408842
11	1	0	-4.147032	1.999554	-0.136260
12	6	0	0.208684	0.415140	-0.287156
13	1	0	0.637860	0.562958	0.754045
14	1	0	0.405665	1.367848	-0.799100

15	6	0	1.076640	-0.706059	-0.848086
16	1	0	0.991322	-1.632316	-0.266501
17	1	0	0.834966	-0.907522	-1.898344
18	8	0	2.475341	-0.321450	-0.880026
19	6	0	3.056956	0.042047	0.274722
20	8	0	2.432713	0.173995	1.329480
21	6	0	4.528742	0.267304	0.139876
22	1	0	4.934302	0.674420	1.069388
23	1	0	4.718747	0.953881	-0.695405
24	1	0	5.015879	-0.689076	-0.094947

Rotational constants (GHZ): 2.9948118 0.3809636 0.3682457

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12.10) EXPERIMENTAL DETAILS FOR CHAPTER 11

General:

Unless otherwise stated, all ^{1}H, ^{13}C, and ^{19}F spectra were acquired on either a BRUKER 300 MHz or 400 MHz NMR in $CDCl_3$ at room temperature. All solvents and reagents were dried and purified using standard methods. Fluorination of various cyclopropanol derivatives was carried out under anhydrous conditions in a nitrogen atmosphere. The chemical shifts, δ, for the spectra were reported in parts per million (ppm) with respect to internal standard tetramethylsilane (TMS δ = 0.00) and 3-chlorobenzotrifluoride (δ -64.2 ppm relative to $CFCl_3$). NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dm = doublet of multiplet), coupling constant in Hz, integration). Crude spectra of compound **126** are reported due to volatility. Compounds **120** and **122** are reported as major β-fluorinated products isolated with minor fluorinated byproducts. Compounds **126**[321] and **130**[104] have been previously reported in the literature. The spectra data were processed with ACD/NMR Processor Academic Edition.[267]

[321] S. Hamman, C. G. Beguin, *Tetrahedron. Lett.* **1983**, *1*, 57-60. b) J. A. Brocks, R. Kosfeld, P. Sartor, M. Schmeiβer, *Chem. Ber*. **1970**, *103*, 1692-1700.

Synthesis of 1-substituted cyclopropanols [322]

I) From methyl esters [250a]

The methyl ester (25 mmol, 1.0 equiv.) was dissolved in anhydrous ether in a flame dried round bottom flask equipped with stir bar. $Ti(i\text{-}OPr)_3Cl$ (5 mmol, 20 mol%) was added to the flask followed by drop wise addition of a 2.0 M solution of EtMgBr in Et_2O (50 mmol, 2.0 equiv.) at room temperature. The reaction solution was stirred overnight under nitrogen (~14 hrs). The solution was cooled to 0°C and was quenched with 10% aqueous H_2SO_4. The organic layer was extracted with Et_2O, washed with DI water, dried with $MgSO_4$, and filtered though Celite. The reaction mixture was concentrated and purified by column chromatography on silica using ethyl acetate/hexanes as eluent.

II) From alkenes[250b]

Cyclohexylmagnesium bromide (45 mmol, 4.5 equiv., 2.0 M in Et_2O) was added drop wise to a solution of ethyl acetate (10 mmol, 1.0 equivalent), olefin (15 mmol, 1.5 equivalent) and $Ti(i\text{-}OPr)_3Cl$ (10 mmol, 1.0 equivalent, 1.0 M in hexanes) in anhydrous THF in a flame dried round bottom flask equipped with stir bar under N_2. The reaction solution was stirred overnight at room temperature under nitrogen atmosphere (~14 hrs). The reaction was quenched with DI water,

[322] Adapted from: a) O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis*, **1990**, 234. b) J. Lee, H. Kim, J. K. Cha, *J. Am. Chem. Soc*. **1996**, *118*, 4198-4199. c) F. Romanov-Michailids, L. Guênêe, A. Alexakis, *Org. Lett.* **2013**, *22*, 5890-5893.

extracted into Et_2O, washed with brine, dried with $MgSO_4$, and filtered through Celite. The reaction mixture was concentrated and purified by column chromatography on silica using ethyl acetate/hexanes as eluent.

III) Synthesis of cyclopropanol for compound 126[250c]

(1-Ethoxycyclopropoxy)trimethylsilane (5.8 ml) was dissolved in methanol under nitrogen in a flame dried round bottom flask and stirred overnight. The reaction mixture was concentrated to afford 1-ethoxy-cyclopropanol, which was fluorinated without further purification.

Ring Opening of Cyclopropanols to form β-Fluorinated Products

Selectfluor (195 mg, 0.55 mmol, 2.2. equiv.) and either 1,2,4,5-tetracyanobenzene (4.45 mg, 0.025 mmol, 0.10 equiv.) or xanthone (5.00 mg, 0.025 mmol, 0.10 equiv.) were added to a 10 ml microwave vial equipped with stir bar under a nitrogen atmosphere. Anhydrous acetonitrile (3 mL) was added; the reaction solution was stirred. The respective cyclopropanol (0.25 mmol, 1.0 equiv.) was added to the vial, and the reaction mixture was irradiated with a UV Pen Lamp at 302 nm for ~16 hours. The reaction mixture was diluted with CH_2Cl_2, washed with 1M HCl, washed with saturated $NaHCO_3$, dried with $MgSO_4$, filtered through Celite, and concentrated. The crude mixture was subjected to column chromatography on florisil using a slightly acidified mixture of ethyl acetate/hexanes with a few drops of conc. HCl as eluent.

Characterization Data

4-cyclohexyl-4-fluorobutan-2-one (115). ^{1}H NMR ($CDCl_3$): δ 4.75 (dm, *J* = 47.8 Hz, 1H), 2.80 (dt, *J* = 9.2, 7.2 Hz, 1H), 2.55 (ddd, *J* = 35.8, 16.4, 3.4 Hz, 1H), 2.20 (s, 3H), 1.90-0.85 (m, 11H); ^{13}C NMR ($CDCl_3$): 206.24 (d, *J* = 2.20 Hz), 93.61 (d, *J* = 171.3 Hz), 46.17 (d, *J* = 24.9 Hz), 41.96 (19.0 Hz), 31.0, 30.95 (d, *J* = 3.7 Hz), 28.38 (d, *J* = 8.1 Hz), 27.41, 26.19, 25.79; ^{19}F NMR ($CDCl_3$): -184.72 (m, *J* = 47.4 Hz, 1F).

4-cyclopentyl-4-fluorobutan-2-one (116). ^{1}H NMR ($CDCl_3$): δ 4.78 (dddd, *J* = 48.4, 8.9, 7.2, 3.0 Hz, 1H), 2.82 (dt, *J* = 15.6, 8.9 Hz, 1H), 2.6 (ddd, *J* = 35.2, 16.2, 3.0 Hz, 1H), 2.23 (s, 3H), 1.96-0.99 (m, 9H); ^{13}C NMR ($CDCl_3$): 206. 06 (d, *J* =2.4 Hz), 93.08 (d, *J* = 170.5 Hz), 48.0 (d, *J* = 24.5 Hz), 44.96 (d, *J* =19.76 Hz), 32.53 30.93, 28.44, 27.94, 25.60; ^{19}F NMR ($CDCl_3$): -180.52 (m, *J* = 49.5 Hz, 1F).

4-cyclooctyl-4-fluorobutan-2-one (117). ^{1}H NMR ($CDCl_3$): δ 4.75 (dm, *J* = 47.8 Hz, 1H), 2.77 (dt, *J* = 8.9, 7.0 Hz, 1H), 2.50 (ddd, *J* = 36.17, 13.19, 2.8 Hz, 1H), 2.20 (s, 3H), 1.85-1.20 (m, 15H); ^{13}C NMR ($CDCl_3$): 206.23 (d, *J* = 2.2 Hz), 94.15 (d, *J* = 172.0 Hz), 46.0 (d *J* = 23.4 Hz), 41.32 (d, *J* = 18.3 Hz), 30.89, 28.69 (d, *J* = 3.7 Hz), 27.17 (d, *J* = 5.9 Hz), 26.74, 26.50, 25.81, 25.54; ^{19}F NMR ($CDCl_3$): -182.05 (m, *J* = 48.5 Hz, 1F).

5-cyclopentyl-4-fluoropentan-2-one (118). ^{1}H NMR ($CDCl_3$): δ 4.95 (dm, *J* = 48.4 Hz, 1H), 2.82 (dt, *J* = 16.2, 7.9 Hz, 1H), 2.58 (dddd, *J* = 30.7, 12.2, 10.2, 4.0 Hz, 1H), 2.19 (s, 3H), 1.99-1.04 (m, 11H); ^{13}C NMR ($CDCl_3$): 205.83 (d, *J* = 3.7 Hz), 89.84 (d, *J* = 167.60 Hz), 49.18 (d, *J* = 22.7 Hz), 41.30 (s, *J* = 20.5 Hz), 36.28 (d, *J* = 3.7 Hz), 33.02, 32.37, 30.90, 25.01, 24.88; ^{19}F NMR ($CDCl_3$): -179.65 (m, *J* = 49.5 Hz, 1F).

5-cyclohexyl-4-fluoropentan-2-one (119). ^{1}H NMR ($CDCl_3$): δ 5.03 (dm, *J* = 49.5 Hz, 1H), 2.91-2.74 (dt, *J* = 15.8, 8.1 Hz, 1H), 2.64-2.43 (dddd, *J* = 30.52, 12.6, 10.0, 4.0 Hz, 1H), 2.19 (s, 3H), 1.86-0.85 (m, 13H); ^{13}C NMR ($CDCl_3$): 205.75 (d, *J* = 3.7 Hz), 88.29 (d, *J* = 166.86 Hz), 49.30 (d, *J* = 22.7 Hz), 42.71 (d, *J* =20.49), 33.87, 33.80, 32.65, 30.84, 26.39, 26.20, 26.03; ^{19}F NMR ($CDCl_3$): -179.40 (m, *J* = 49.5 Hz).

4-fluoro-6-phenylhexan-2-one (120). ^{1}H NMR ($CDCl_3$): δ 7.46-7.18 (m, 5H), 4.99 (ddt, *J* = 48.5, 12.1, 4.1 Hz), 3.03-2.48 (m, 4H), 2.18 (s, 3H), 2.08-1.76 (m, 2H); ^{13}C NMR ($CDCl_3$): 205.44 (d, *J* = 4.4 Hz), 140.98, 128.55, 128.53, 128.51, 128.43, 126.13, 89.29 (d, *J* = 168.1 Hz), 48.73 (d, *J* = 22.1 Hz), 36.78 (d, *J* = 20.6 Hz), 31.17, 30.84; ^{19}F NMR ($CDCl_3$): -181.4 (m, *J* = 48.2 Hz, 1F).

4-fluoro-5-(naphthalen-1-yl)penta-2-one (121). ^{1}H NMR ($CDCl_3$): δ 8.0 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.55-6.89 (m, 4H),

5.26 (dm, *J* = 47.5 Hz, 1H), 3.36 (m, 2H), 2.85 (m, 1H), 2.59 (dddd, *J*= 27.7, 17.0, 11.9, 4.7 Hz), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$): 205.51 (d, *J* = 5.1 Hz), 133.94, 132.14, 128.88, 128.0, 127.80, 126.34, 125.78, 125.46, 123.73, 89.69 (d, *J* = 172.0 Hz), 48.24 (d, *J* = 22.7 Hz), 38.18 (d, *J* = 22.0 Hz), 30.82 (d, *J* = 1.5 Hz); ^{19}F NMR ($CDCl_3$): -176.35 (m, *J* = 48.4 Hz, 1F).

4-fluoro-5-phenylpentan-2-one (122). ^{1}H NMR ($CDCl_3$): δ 7.30-7.07 (m, 5H), 5.11 (dm, *J* = 47.4 Hz, 1H), 2.99-2.30 (m, 4H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$): 205.5 (d, *J* = 3.7 Hz), 136.27, 129.5, 128.6, 126.9, 90.95 (d, *J* = 171.0 Hz), 47.86 (d, *J* = 22.9 Hz), 41.08 (d, *J* = 21.4 Hz), 30.8; ^{19}F NMR ($CDCl_3$): - 177.96 (m, *J* = 47.1 Hz).

4-fluorodecan-2-one (123). ^{1}H NMR ($CDCl_3$): δ 4.95 (dm, *J* = 48.4 Hz, 1H), 2.85 (m, 1H), 2.57 (dddd, *J* = 30.89, 12.24, 10.39, 4.14 Hz, 1H), 1.70-1.20 (m, 10H), 0.90 (t, *J* = 7.0, 3H); ^{13}C NMR ($CDCl_3$): 205.79 (d, *J* = 3.7 Hz), 90.13 (d, *J* = 168.3 Hz), 48.78 (d, 23.4 Hz), 35.02 (d, *J* = 20.5 Hz), 31.64, 30.90, 28.95, 22.81 (d, *J* = 4.4 Hz), 22.51, 14.01; ^{19}F NMR ($CDCl_3$): -179.55 (m, *J* = 47.4 Hz).

4-fluorotetradecan-2-one (124). ^{1}H NMR ($CDCl_3$): δ 4.96 (dm, *J* = 48.2 Hz, 1H), 2.86 (m, 1H), 2.58 (m, 1H), 2.22 (s, 3H), 1.60-1.20 (m, 18H), 0.90 (t, *J* = 7.0Hz, 3H); ^{13}C NMR ($CDCl_3$): 205.79 (d, *J* = 3.7 Hz), 90.17 (d, *J* = 167.6 Hz), 48.82 (d, *J* = 22.7 Hz), 35.05 (d, *J* = 20.5 Hz), 32.0, 30.88, 29.53, 29.31, 24.85 (d, *J* = 4.4 Hz), 22.68, 14.10; ^{19}F NMR ($CDCl_3$): -180.0 (m, *J* = 47.4 Hz, 1F).

4-fluoroicosan-2-one (125). ^{1}H NMR ($CDCl_3$): δ 4.97 (dm, *J* = 48.4 Hz, 1H), 2.87 (dt, *J* = 23.9, 8.1 Hz, 1H), 2.59 (dddd, *J* = 26.3, 12.3, 9.9, 4.1 Hz, 1H), 2.22 (s, 3H), 1.77-1.20 (m, 28H), 0.9 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): 205.74 (d, *J* = 4.4 Hz), 90.17 (d, *J* = 168.1 Hz), 48.83 (d, *J* = 22.9 Hz), 35.06 (d, *J* = 20.64 Hz), 31.9, 29.7, 29.6, 29.51, 29.34, 24.88, 22.7, 14.1; ^{19}F NMR ($CDCl_3$): -179.57 (m, *J* = 48.2 Hz, 1F).

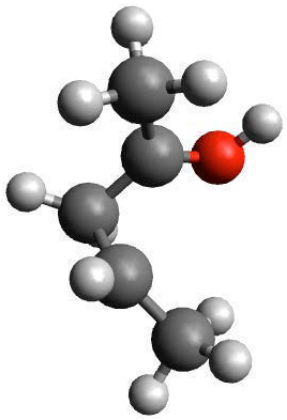
Ethyl 3-fluoropropanoate (126). ^{1}H NMR ($CDCl_3$): δ 4.61 (dt, *J* = 46.5, 5.8 Hz, 2H), 4.01 (m, 2H), 2.60 (m, 2H), 1.17 (t, *J* = 7.30 Hz); ^{19}F NMR ($CDCl_3$): -218.65 (m, *J* = 46.4 Hz, 1F).

(5*R*,10*S*,13*R*)-17-((*S*)-7-fluoro-5-oxoheptan-2-yl)-10,13-dimethyltetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3(2*H*)-one (127): ^{1}H NMR ($CDCl_3$): δ 4.72 (dt, *J* = 46.5, 6.1 Hz, 2H), 2.83 (m, 2H), 2.65 (m, 2H), 2.42-1.20 (m, 26H), 1.04 (s, 3H), 0.94 (d, *J* = , 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$): 213.47, 208.1 (d, *J* = 4.4 Hz), 79.1 (d, *J* = 165.1 Hz), 56.44, 56.02, 44.32, 42.96, 42.78, 42.37, 40.73, 40.49, 40.05, 37.12 (d, *J* = 21.18 Hz), 35.53, 35.24, 34.89, 29.39, 28.19, 26.61, 25.77, 24.16, 22.66, 21.19, 18.43, 12.08, 7.8; ^{19}F NMR ($CDCl_3$): -219.82 (m, *J* = 46.5 Hz, 1F)

1-cyclohexyl-3-fluoropropan-1-one (128). ^{1}H NMR ($CDCl_3$): δ 4.73 (dt, *J* = 46.7,6.1 Hz, 2H), 2.85 (dt, *J* = 24.0, 5.8 Hz, 2H), 2.38 (m, 1H), 1.93-0.85 (m,

10H); ^{13}C NMR ($CDCl_3$): 210.59 (d, J = 4.4 Hz), 79.20 (d, J = 164.4 Hz), 51.22, 40.68 (d, J = 21.4 Hz), 28.10, 25.79, 25.54; ^{19}F NMR ($CDCl_3$): -220.11 (m, J = 46.4 Hz, 1F).

3-fluorocycloheptanone (130): ^{1}H NMR ($CDCl_3$): δ 4.82 (dm, J = 46.4 Hz, 1H), 2.97-2.69 (m, 2H), 2.53-2.34 (m, 2H), 2.10 (m, 2H), 1.92-0.59 (m, 4H); ^{13}C NMR ($CDCl_3$): 209.58, 88.59 (d, J = 171.3 Hz), 49.4 (d, J = 23.4 Hz), 44.44, 35.69 (d, J = 20.49 Hz), 23.78, 23.65; ^{19}F NMR ($CDCl_3$): -175.56 (m, J = 46.4 Hz, 1F).



trans-1,2-dimethylcyclopropanol radical cation

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opt wb97xd/cc-pvtz scrf=(solvent=acetonitrile) maxdisk=29GB geom=connectivity

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Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.768450	0.088797	-0.203022
2	6	0	0.200811	-0.608933	-1.064533
3	6	0	1.055105	-0.693351	0.149077
4	1	0	0.603059	0.024799	-1.847554
5	1	0	-0.160381	-1.567645	-1.420306
6	1	0	0.916786	-1.543229	0.802724
7	8	0	-0.708952	1.387681	-0.221722
8	1	0	-1.282401	1.790853	0.443355
9	6	0	-1.805798	-0.600480	0.593517
10	1	0	-1.891160	-0.169570	1.590677
11	1	0	-1.612853	-1.665709	0.665771
12	1	0	-2.760142	-0.455032	0.079606
13	6	0	2.100535	0.292450	0.466149
14	1	0	2.130755	0.511788	1.533036
15	1	0	1.991691	1.213873	-0.101516
16	1	0	3.069396	-0.150292	0.207739

VITA

Steven Patrick Bloom was born October 15, 1988 in Baltimore, Maryland to Johnathon and Deborah Bloom. After grade school at Youths Benefit Elementary and high school at Fallston, Steve moved to Westminster, Maryland to attend McDaniel College. An undecided major at first, Steve dabbled in a variety of subjects ranging from Biology to Biochemistry, Spanish, English, and even Art. It wasn't until Steve began his coursework in Organic chemistry in the Spring of 2008 that he found his true calling. Over the next few years, Steve studied under the tutelage of Professor Richard H. Smith and Professor Peter Craig honing his skills in the classroom and gaining valuable research experinece. During his summers, Steve also interned at Aberdeen Proving Grounds and Egdewood Arsenal where he conducted research in analytical and environmental chemistry.

Having developed an appetite for research, especially in the areas of organic and organometallic chemistry, Steve decided to attend grauate school at Johns Hopkins University. Two weeks after graduating with his BA, Steve decided he was too bored (possibly excited) to wait until the following academic year and joined the Lectka group in the Summer of 2010. During his graduate school career, Steve has aspired to develop new, and often radically different methods for the site-selective incorporation of fluorine into organic molecules, a love-hate relationship to say the least. He hopes that one day the chemistry he has

developed will be used for the industrial production of fluorinated pharmaceuticals, agrochemicals, and more.

After receiving his PhD in February 2015, Steve will enjoy a much needed vacation before beginning postdoctoral studies at Princeton University with Professor David MacMillan.

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